haematologica
Journal of the Ferrata Storti Foundation

HLA-haploidentical hematopoietic stem cell transplantation in patients with sickle cell disease: results from the phase II DREP-HAPLO trial

by Nathalie Dhédin, Bénédicte Bruno, Catherine Paillard, Erasti Gounfle, Nimrod Buchbinder, Marie Ouachée Chardin, Mabel Gaba, Jean-Benoît Arlet, Cécile Arnaud, Camille Jung and Corinne Pondarré

Received: October 7, 2025.
Accepted: December 2, 2025.

Citation: Nathalie Dhédin, Bénédicte Bruno, Catherine Paillard, Erasti Gounfle, Nimrod Buchbinder, Marie Ouachée Chardin, Mabel Gaba, Jean-Benoît Arlet, Cécile Arnaud, Camille Jung and Corinne Pondarré. HLA-haploidentical hematopoietic stem cell transplantation in patients with sickle cell disease: results from the phase II DREP-HAPLO trial.
Haematologica. 2025 Dec 11. doi: 10.3324/haematol.2025.300013 [Epub ahead of print]

HLA-haploidentical hematopoietic stem cell transplantation in patients with sickle cell disease: results from the phase II DREP-HAPLO trial

Nathalie Dhédin[1,2], Bénédicte Bruno[3], Catherine Paillard[4], Erasti Gounfle[5], Nimnrod Buchbinder[6], Marie Ouachée Chardin[7], Mabel Gaba[5], Jean-Benoît Arlet[8], Cécile Arnaud[9], Camille Jung[5,10], Corinne Pondarré[11]

Affiliations.

1. Adolescent and Young Adult Hematology Unit, Saint Louis University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France.
2. Epidemiology and Clinical Statistics for Trials & Real-world evidence Research (ECSTRRA), Saint Louis Research Institute, UMR1342, INSERM, Université de Paris, France.
3. Paediatric Hematology, F-59000 Lille, France.
4. Department of Paediatric Haematology and Oncology, Strasbourg University Hospital, Strasbourg, France; Strasbourg University, INSERM, IRM UMR-S 1109, F-67000 Strasbourg, France
5. Department of Health Research and Innovation, Intercommunal Hospital Center of Créteil, Créteil, France
6. Department of Paediatric Haematology and Oncology, Charles Nicolle University Hospital, Rouen, France.
7. Institute of Pediatric Oncology and Hematology, Lyon, France
8. French Sickle Cell Referral Center, Internal Medicine Department, Georges Pompidou European Hospital, and Paris University, Paris, France.

9. Pediatric department Sickle Cell Referral Center, Centre Hospitalier Intercommunal de Créteil, France
10. Pediatric department Intercommunal Hospital Center of Créteil and University Paris-Est Créteil, Créteil, France
11. Intercommunal Hospital Center of Créteil, INSERM U955, IMRB, Paris XII University, Créteil, France

Author Contributions:

ND designed the study, recruited patients, contributed to the analysis, and wrote the manuscript. BB, CPa, NB, MOC, JBA, and CP recruited patients and critically revised the manuscript. EG performed the data analysis. MG collected the data. CJ contributed to the study design, data curation and analysis.

Running heads.: Haploidentical transplant in sickle cell disease.

Corresponding author:

Dr N Dhédin. Adolescent and Young Adult Hematology Unit. Hôpital Saint Louis. 1 avenue Claude Vellefaux. 75010 Paris. Tel: +33 1 42 38 51 27. E-mail: nathalie.dhedin@aphp.fr

Data sharing statement : Anonymized data will be available upon reasonable request.

Trial registration. ClinicalTrials.gov: NCT03240731

Keywords: Sickle cell disease, Haploidentical, Post-transplant cyclophosphamide, Thiotepa

Authors' disclosures

Kheocyt provided funding (34000€) to cover the additional costs of the clinical study. No direct financial compensation was given to the investigators for conducting this study. The authors declare no other conflicts of interest

Funding statement

This study was funded by the Centre Hospitalier Intercommunal de Créteil (CHIC) and Kheocyt. Kheocyt provided financial support for the study but had no role in the study design, data collection and management, or analysis.

Acknowledgements. We thank Keocyt for its financial support of 34 000 euros.

Abstract :

We report the final analysis of the Drep-Haplo multicenter phase 2 protocol, which evaluated haploidentical transplantation after reduced-intensity conditioning regimen incorporating thiotepa, in children and adults with severe sickle cell disease (SCD). Twenty-two patients (median age: 17 years; range: 12–40) received a conditioning regimen consisting of 2 Gy total body irradiation, thymoglobulin, cyclophosphamide, fludarabine, and thiotepa, followed by T cell–replete bone marrow infusion and graft-versus-host disease (GVHD) prophylaxis based on post-transplant cyclophosphamide.

The primary endpoint, event-free survival, defined as survival without graft failure and without moderate-to-severe chronic GVHD, was 68.18% (95% CI: 51.25%–90.70%) and 61.98% (95% CI: 44.07%–87.19%) at 1 and 4 years, respectively. Overall survival and rejection-free survival at 4 years were 90.15% (95% CI: 78.03%–100%) and 85.56% (95% CI: 71.63%–100%), respectively. Six patients (27%) developed moderate-to-severe GVHD. In most cases (4/6), GVHD resolved, leaving only two patients (9%) with persistent moderate to severe GVHD at last follow-up. Eighty-five grade 2 to 4 infectious episodes were reported in 21 patients during the 24 months of follow-up, most of which were bacterial (38 cases). These data strengthen existing evidence supporting the feasibility of haploidentical transplantation in both pediatric and adult patients with severe SCD, demonstrating a very low rejection rate when thiotepa is incorporated into the conditioning regimen. Future efforts should focus on reducing chronic GVHD and infection rates.

Introduction

Sickle cell disease (SCD) is a severe inherited hemoglobinopathy associated with hemolytic anemia, recurrent vaso-occlusive episodes, and cumulative end-organ damages, leading to significantly impaired quality of life and premature mortality. To date, allogeneic hematopoietic stem cell transplantation (HSCT) remains the only established curative treatment for SCD. In children, myeloablative HSCT from an HLA-identical sibling donor offers excellent rate of survival without disease .[1,2] In adult patients, nonmyeloablative conditioning regimens have been developed to reduce toxicity while preserving curative potential. [3,4] Nonetheless, a major barrier to the widespread application of HSCT in SCD remains the limited availability of HLA-identical sibling donors

Haploidentical transplantation has emerged as a compelling alternative, substantially expanding donor availability. Initial reduced intensity conditioning (RIC) haploidentical transplant platforms using fludarabine, cyclophosphamide, thymoglobulin and 2 grays total body irradiation (TBI) with GVHD prophylaxis based on post-transplant cyclophosphamide (PTCy) demonstrated favorable safety profiles, with low incidence of GVHD but rate of graft failure, approaching 50%.[5] To address this limitation, several modifications to the original PTCy-based regimen have been investigated. [6-9] The approach of intensifying conditioning with thiotepa has been the most widely used. [10,11] We hereby report the final analysis of Drep-Haplo a French multicenter phase 2 protocol, including both children and adults, that employs an approach of RIC haploidentical transplantation with conditioning intensification with thiotepa.

Methods

Study design and participants

Drep-Haplo is a prospective, multicenter phase 2 clinical trial (ClinicalTrials.gov: NCT03240731) designed to evaluate the efficacy and safety of haploidentical HSCT in patients with severe SCD. The

trial was sponsored by the Centre Hospitalier Intercommunal de Créteil (France) and was approved by the institutional review board (N° ID-RCB: 2016-A00300-51). Eligibility criteria were: patients aged from 7 to 40 years with SCD (HbSS) or Sβ^o-thalassemia, with no available HLA-identical sibling donor. Patients were required to have at least one severe SCD-related complication detailed in supplementary methods. All collected data have been reviewed by the sponsor. During the course of the study, an independent Data Safety Monitoring Board (DSMB) met regularly to validate the continuation of the study and to analyze serious adverse events. All patients and donors gave informed consent.

Procedures

Transplant modalities

Pre-Transplant recipient management is detailed in **supplemental methods**. Conditioning included thymoglobulin 4.5 mg/kg; thiotepa 10 mg/kg, cyclophosphamide 29 mg/kg, fludarabine 150 mg/m^2 and 200-cGy TBI with testis shielding in men. GVHD prophylaxis included PTCy (50 mg/kg on days +3 and +4), mycophenolate mofetil (day +5 through day +35); and sirolimus targeting (day +5 through day +365) post transplantation.[7] Stem cell source was bone marrow in all recipients **(supplemental Figure 1).**

Outcomes and definitions

The primary endpoint was 12-month event-free survival (EFS), defined as survival without rejection and without moderate to severe chronic GVHD (cGVHD). Secondary outcomes included overall survival (OS), engraftment rates, graft rejection, rejection-free survival (RFS) defined by survival without rejection, GVHD, infections, hemolysis markers, chimerism. In accordance with the protocol, each participant had a 24-month follow-up, and the main outcome was also updated in October 2024. Graft failure was defined as donor total peripheral blood cell chimerism below 5%, low mixed chimerism as

5 to 50% donor blood cells, high mixed chimerism as 50 to 95% donor blood cells and full donor chimerism as donor blood cells above 95%. The severity of adverse events including infections was recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. PedsQL Disease-Specific Modules. Quality of life was assessed using the French version of the Pediatric Quality of Life Inventory Generic Core Scales, Version 4.0 (PedsQL 4.0) self-report for patients under 18 years of age, and the EORTC QLQ-C30, Version 3.0 self-report for patients aged 18 years and older. Scores are transformed to a 0–100 scale, with higher scores indicating better quality of life. [12,13]

Statistical analysis

Categorical variables were summarized as counts and percentages, and continuous variables as medians with interquartile ranges (IQRs). EFS, OS and survival without rejection were estimated using the Kaplan-Meier method. All statistical analyses were conducted using R software, version 4.4.3.

Protocol evolution

The original use of G-CSF–mobilized marrow was discontinued due to concerns about increased GVHD risk (Two of the 3 patients who received a G-CSF-primed bone marrow developed cGVHD). The protocol was planned to include 15 patients but the duration of inclusion was extended. Initial eligibility criteria included patients aged 13 years and older; this was subsequently revised to allow the inclusion of children aged 7 years and above.

Results

Study population

A total of 25 patients were enrolled across five French centers between September 2017 and April 2022. Three patients did not proceed to transplantation: one was considered a screening failure

because he presented with cerebrovascular vasculopathy but had not initiated a transfusion program; one whose donor withdrew consent after enrollment; and one with a history of delayed hemolytic transfusion reaction contraindicating further transfusions, resulting in 22 patients who proceeded to transplantation per protocol. l. The median age at transplant was 17 years (IQR: 16–19; range: 12–40), 13 patients were under 18-year-old at transplant and 9 higher. Sixty height % were females. SCD genotypes included HbSS (95%) and HbSβ^o (5%). Prior to transplant, 86% had recurrent VOCs, 50% had experienced at least one ACS and 50% had cerebral arterial stenosis. Delayed hemolytic transfusion reactions were reported in 14% of patients. Hydroxyurea had been administered in 77% of patients, and 73% of patients were on chronic red blood cell transfusions (9 by simple transfusions, 5 by erythrocytapheresis, and 2 who had received both modalities). Among these 16 patients, three had normal ferritin levels and did not undergo liver MRI. Among the remaining 13, liver iron concentration was normal (<2 mg of iron per gram of liver tissue) in two patients, between 2 and 7 mg in 8 patients, and between 7 and 10 mg in the remaining three patients. Patients experienced a median of 5 [IQR: 1–12] hospitalizations during the 3 years preceding transplant. Most donors (n=19; 86%) were heterozygous for HbS (HbAS). Patient characteristics are summarized in **Table 1**.

Outcomes

The primary endpoint, one-year EFS, defined as survival without graft failure and without moderate-to-severe cGVHD was 68.18% (95%CI: 51.25%-90.70%). With a median follow-up of 4.25 years [IQR: 3.25–5.16], the 4-year EFS was 61.98% (95%CI: 44.07%-87.19%). OS at 1 and 4 years were 95,45% (95%CI: 87.14%-100%) and 90.15% (95%CI : 78.03%-100%) respectively. Rejection-free survival at 1 and 4 years were 90.90% (95%CI: 79.66%-100%) and 85.56% (95%CI: 71.63%-100%) respectively. **(Figure 1).** All patients achieved engraftment, but one patient (4.5%) aged 17 years at transplant who received 2.67X10^6 CD34+ cells/kg, experienced secondary graft failure, occurring at 4.5 months post-transplant in the context of SARS-CoV-2 infection. Two patients (9%) died: one, aged 19.7 years, from

cGVHD (8 months post-transplant) and the other, aged 16 years, from a late fulminant pneumococcal sepsis (31 months post-transplant).

Hematopoietic recovery

The median time to neutrophil recovery was 21 days [IQR: 19–25]. The median times from transplantation to the last red blood cell and platelet transfusions were 27 days [IQR: 19–35] and 24 days [IQR: 17–31], respectively. Median CD4+ T cell counts were 0.4×10^9/L at 3 months [IQR: 0.1–0.7] and 0.6×10^9/L at 12 months [IQR: 0.4–1.0].

Graft-versus-Host Disease

Acute GVHD occurred in 9 patients (40.9%): grade II in 6 (27.2%), grade III in 2 (9%), and grade IV in 1 (4.5%). Chronic GVHD was observed in 8 patients (36%): mild in 2 (9%), moderate in 3 (13.5%), and severe in 3 (13.5%). The 2-year incidence of moderate to severe cGVHD was 27%. Two of the three patients who received a G-CSF-primed bone marrow experienced cGVHD (moderate : N=1, severe : N=1). At the last follow-up, moderate-to-severe cGVHD was present in 9% of patients, after resolution in 4 of the 6 initially affected cases. Only one patient continued to require systemic immunosuppressive therapy.

Infections

A total of 85 infectious episodes were reported in 21 patients, within the first 24 months post-transplant: 51 were grade 2, 32 grade 3 and 2 grade 4 according to the CTCAE Version 5.0. Patients with grade II-IV aGVHD or moderate-to-severe cGVHD presented a median of 4 (range 0-7) infection episodes versus 3 (range 1-9) in patients without GVHD. The most common infections were bacterial

(38 cases), mostly bloodstream infections or severe sepsis (29 cases). Among these, 6 episodes were caused by *Pseudomonas aeruginosa* and 6 by *Staphylococcus aureus*. In 8 patients, the infection was linked to the central venous catheter. Two non-splenectomized patients experienced *Streptococcus pneumoniae* infections: one developed pneumonia, and another, whose infection occurred after 24 months and was therefore not included in the main count, died from fulminant pneumococcal sepsis. This patient had discontinued pneumococcal prophylactic antibiotics and had received revaccination after transplantation; however, the sepsis was caused by pneumococcal serotype 24F, which was not covered by the vaccine.Four patients experienced BK virus-associated cystitis. Most infections occurred early after transplant with only 17.6% after day 100. No cases of cytomegalovirus (CMV) disease or post-transplant lymphoproliferative disorder (PTLD) were observed. Infectious episodes are detailed on the **Supplemental Table 1**.

Others post-transplant complications

Three patients (13.5%) developed posterior reversible encephalopathy syndrome (PRES), concomitant with corticosteroid therapy used for the management of GVHD or for treatment of macrophage activation syndrome (MAS). MAS occurred in two patients (9%), one of whom presented with disseminated human herpesvirus 6 (HHV-6) infection. No new SCD-related complications were reported post-transplant. Although follow-up remains relatively short, no cases of myeloid malignancy have been identified to date.

Follow-up biological data

In the absence of rejection, hemoglobin levels rapidly normalized post-transplant, and hemolytic markers were corrected by 3 months. A key biological marker of cure was the HbS level, which mirrored the donor's phenotype: 0% in the recipient of AA donor and <40% in those with AS donors. Among the

21 patients who did not reject complete donor chimerism was observed in 19 patients, at 2-year post-transplant and at the last follow-up (median: 34 months, [IQR: 27-51]). The remaining 2 patients exhibited mixed chimerism, 75% and 45% respectively at 24 months and 47% and 36% respectively at the last follow-up (57 and 52 months post-transplant). Importantly, despite mixed chimerism, hemolytic markers remained normal, with HbS levels and both Hb AS donors (of 37.2% and 38.3%). **(Table 2)**

Quality of life reports

Self-reports were obtained pre-transplant in 9 of the 14 patients younger than 18 years and in all 8 adult patients. One adult who died 8 months post-transplant was not evaluable at 12 and 24 months. Two participants who turned 18 during follow-up initially completed the pediatric self-report and subsequently switched to the adult version. The analysis showed an improvement in total scores after transplant, with more pronounced gains in adolescent self-reports compared with those of adults. Interestingly, pre-transplant physical scores were lower in adolescents than in adults with substantial improvement observed in adolescents after transplant. In both groups, emotional scores improved post-transplant. Fatigue remained a long-lasting symptom after transplant in adults. Pain scores showed only slight improvement, but most patients had been enrolled in a chronic transfusion exchange program prior to transplant, and therefore may have had relatively few pain crises at baseline **(Table 3).**

Discussion

This is the third multicenter phase 2 trial evaluating reduced-intensity haploidentical transplantation incorporating thiotepa in patients with severe SCD. The first study was an international collaborative consortium including both pediatric and adult patients across eight centers, totalizing 70 transplants with varying eligibility criteria.[10] The second was a prospective multicenter united States (U.S) study

involving 42 patients over 15 years of age with severe SCD-related complications, such as cerebral vasculopathy, recurrent VOCs or ACS.[11] As in previous studies, our findings confirm that adding thiotepa is critical for engraftment. The graft failure rate was notably low, with only one secondary graft failure (4.5%). While the consortium study observed a 25% rejection rate in patients under 18 years of age compared to 0% in adults, this was not confirmed in our cohort: from 13 patients under 18-year-old at transplant and 9 adults, a single rejection was observed in a 17-year-old patient. In the international consortium study, 6 of the 8 patients who experienced graft rejection also presented viral infections, supporting the hypothesis that infections may have contributed to rejection.[10] In the absence of rejection, 18 of 20 patients achieved sustained full donor chimerism at two years and last follow-up, with normalization of hemolysis and HbS levels matching those of the donor, suggesting disease cure. Notably, in the two patients with mixed chimerism, levels of 47% and 36% donor chimerism more than 4 years post-transplant were sufficient to achieve complete resolution of hemolysis and to maintain HbS levels similar to their donors. Although longer follow-up is needed, there is hope that these patients are cured. Additionally, the high rate of full donor chimerism with this regimen suggests a low risk of malignant transformation.

Toxicity management remains a key challenge, particularly regarding transplant-related mortality and chronic GVHD. Our cohort showed a higher incidence of moderate to severe cGVHD than previously reported. No age-related correlation was identified (data not shown), but 2 out of 3 patients (66%) who received G-CSF–primed marrow developed moderate to severe cGVHD, compared to 4/19 (21%) among those receiving non-primed marrow. While most cGVHD cases resolved, one patient remained on systemic immunosuppression at last follow-up. These findings highlight the need for larger studies to assess cGVHD incidence in patients receiving non–G-CSF–primed marrow. If it is confirmed that the incidence of cGVHD remains significant, GVHD prophylaxis could be optimized through strategies such as increasing the ATG dose, which has been shown to reduce cGVHD incidence in children with SCD undergoing matched sibling transplantation, or adding abatacept, as explored in unrelated donor settings. [1,14]

The 4-year mortality rate of 9.8% observed in our study is considered acceptable given the underlying severity of disease in this cohort. . This mortality rate must be weighed against the high cure rate achieved with HSCT. One patient died from pneumococcal sepsis. This patient was not splenectomized (versus three others); however, functional asplenia, nearly universal in adolescents and adults with SCD, complicates interpretation of infection-related mortality, as these patients are intrinsically at increased risk for severe pneumococcal infections regardless of transplant status. The incidence of infections was high, mainly due to bacterial infections, particularly bloodstream infections. Seven cases were clearly catheter-related, often in patients with poor venous access requiring prolonged central lines. More cases were likely underreported. Viral infections were mostly expected post-allograft, with frequent BK virus–associated cystitis. However, six patients developed less common infections such as disseminated adenovirus and HHV-6 requiring antiviral treatment, complications usually reported in patients with profound immunosuppression. This high rate of infections is consistent with data reported in the multicenter U.S. trial and notably all eight deaths across both the U.S. and consortium studies were attributed to infectious complications.[10,11] These findings underscore the critical need for effective infection prophylaxis and comprehensive supportive care in the post-transplant setting.

Although our cohort was smaller than those reported in the two previous studies, it represents the majority of haploidentical transplants performed in France for this indication during the study period, with data rigorously monitored by the sponsor. This reinforces, with longer follow-up, previously published findings and provides detailed information on post-transplant infections. We providedquality-of-life outcomes which suggest that transplantation is associated with a progressive improvement in quality of life, which appears more pronounced at 2 years in adolescents than in adults

The role of haploidentical transplantation in SCD is often compared to that of gene therapy. The main advantage of gene therapy is the absence of GVHD. However, haploidentical transplantation offers several benefits, especially better feasibility and lower cost. In our study, 17 out of 22 patients (77%) would not have qualified for a gene therapy trial due to cerebral vasculopathy requiring exchange

transfusions or a history of transfusion-related complications. Gene therapy also requires a myeloablative conditioning regimen, which may not be suitable for some adults. In addition, the process is more complex, with a higher risk of manufacturing failure: in a recent report 24% of mobilized patients did not receive exa-cel gene therapy.[15] After haploidentical transplant, hemolysis resolves in almost all patients who did not reject while it persists in about 50% of cases after lentiGlobin or exa-cel therapy.[15,16] Thus, haploidentical transplantation has shown it can cure SCD, while gene therapy, so far, mostly improves it.

In conclusion, the data from the Drep-Haplo protocol reinforce existing evidence supporting the feasibility of haploidentical transplantation in both pediatric and adult patients, and its potential to cure the majority of them. However, long-term follow-up is needed to assess data on sickle cell related organ damages and fertility. Compared to prior studies, our findings suggest a trend toward a very low rejection rate, albeit with a higher incidence of cGVHD. A fair comparison of feasibility and outcomes between haploidentical transplantation and gene therapy should be conducted in similar patient populations, using standardized evaluation criteria.

References:

1.Bernaudin F, Dalle JH, Bories D, et al. Long-term event-free survival, chimerism and fertility outcomes in 234 patients with sickle-cell anemia younger than 30 years after myeloablative conditioning and matched-sibling transplantation in France. Haematologica. 2020;105(1):91-101.

2. Cappelli B, Volt F, Tozatto-Maio K, et al. Risk factors and outcomes according to age at transplantation with an HLA-identical sibling for sickle cell disease. Haematologica. 2019;104(12):543-546.

3. Hsieh MM, Kang EM, Fitzhugh CD, et al. Allogeneic hematopoietic stem-cell transplantation for sickle cell disease. N Engl J Med. 2009;361(24):2309-2317.

4. Alzahrani M, Damlaj M, Jeffries N, et al. Non-myeloablative human leukocyte antigen-matched related donor transplantation in sickle cell disease: outcomes from three independent centres. Br J Haematol. 2021;192(4):761-768.

5. Bolaños-Meade J, Fuchs EJ, Luznik L, et al. HLA haploidentical bone marrow transplantation with posttransplant cyclophosphamide expands the donor pool for patients with sickle cell disease. Blood. 2012;120(22):4285-4291.

6. Kharya G, Bakane AN, Agarwal S, Rauthan AM. Pre-transplant myeloid and immune suppression, upfront plerixafor mobilization and post-transplant cyclophosphamide: novel strategy for haploidentical transplant in sickle cell disease. Bone Marrow Transplant. 2021;56(2):492-504.

7. De la Fuente J, Dhedin N, Koyama T, et al. Haploidentical Bone Marrow Transplantation with Post-Transplantation Cyclophosphamide Plus Thiotepa Improves Donor Engraftment in Patients with Sickle Cell Anemia: Results of an International Learning Collaborative. Biol Blood Marrow Transplant. 2019;25(6):1197-1209.

8. Saraf SL, Oh AL, Patel PR, et al. Haploidentical Peripheral Blood Stem Cell Transplantation Demonstrates Stable Engraftment in Adults with Sickle Cell Disease. Biol Blood Marrow Transplant. 2018;24(8):1759-1765.

9. 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):183-193.

10. Kassim AA, de la Fuente J, Nur E, et al. An international learning collaborative phase 2 trial for haploidentical bone marrow transplant in sickle cell disease. Blood. 2024;143(25):2654-2665.

11. Kassim AA, Walters MC, Eapen M, et al. Haploidentical Bone Marrow Transplantation for Sickle Cell Disease. NEJM Evid. 2025;4(3):EVIDoa2400192.

12. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. Med Care. 2001;39(8):800-812.

13. Fayers P, Bottomley A, EORTC Quality of Life Group, Quality of Life Unit. Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. Eur J Cancer. 2002;38 Suppl 4:S125-133.

14. Ngwube A, Shah N, Godder K, Jacobsohn D, Hulbert ML, Shenoy S. Abatacept is effective as GVHD prophylaxis in unrelated donor stem cell transplantation for children with severe sickle cell disease. Blood Adv. 2020;4(16):3894-3899.

15. Frangoul H, Altshuler D, Cappellini D, et al. CRISPR-Cas9 Gene Editing for Sickle Cell. Disease and β-Thalassemia. N Engl J Med. 2021;384(3):252-260.

16. Kanter J, Walters M, Krishnamurti L, et al. Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease. N Engl J Med. 2022;386(7):617-628.

Table 1: Patients characteristics	
	Total N=22 (% or range) [IQR]
Age at transplant, y	
Median (range) [IQR]	17 years (12-40) [16-19]
Sex : Female (%)	15 (68%)
Sickle subtypes	
HbSS	21 (95.5%)
HbS/Β0	1 (4.5%)
Pre-transplant sickle-related complications	
Recurrent vaso-occlusive crisis	19 (86.3%)
Acute chest syndrome	11 (50%)
CNS disease	
Overstroke	5 (22.7%)
Arterial stenosis	11 (50%)
Silent infarct	1 (4.5%)
History of abnormal TCD	3 (13.5%)
Moya Moya	4 (18.1%)
Avascular necrosis	3 (13.5%)
Sickle-related nephropathy	2 (9%)
Presence of micro/macroalbuminuria	2 (9%)
GFR<60ml/mn/1.73m²	0
Tricuspid regurgitation velocity (>2.5m/s)	0
Hospitalization	
Total number of hospitalizations during the last 3 years	5 [1-12]
Prior treatment	
Hydroxyurea	17 (77%)
Regular exchange programs (> 1 year)	16 (73%)
Treatment related complications	
History of DHTR	3 (14%)
Iron overlaod : Ferritin (mg/l)>1000	10 (46%)
Female donor to male recipient:	7 (32%)
ABO recipient-donor type compatibility	
Matched	10 (46%)
Minor incompatibility	6 (27%)
Major incompatibility	6 (27%)
CMV serology : recipient/ donor	
Positive/positive	18 (82%)
Positive/negative	2 (9%)
Negative/positive	1 (4.5%)
Negative/negative	1 (4.5%)
Recipient positive EBV serology	22 (100%)
Donor hemoglobin phenotype	
Hemoglobin AS	19 (86%)
Hemoglobin AA	3 (14%)
Sorror score : med [IQR]	1 [0-2]
G-CSF primed bone marrow	3 (14%)
CD34+ cell dose infused (10^6/kg recipient)	2.67 (1.6-6.8)

CNS: central nervous system, TCD: transcranial doppler ultrasonography. GFR: glomerular filtration rate. DHTR: delayed hemolytic tranfusion reaction. G-CSF: Granulocyte-Colony Stimulating Factor.

Table 2: Biological evolution

Parameters	Month 3	Month 12	Month 24
Nb of patients evaluable	**22**	**21**	**21**
Hemoglobin (g/dl), med [IQR]	11[10-12]	12.5[10.7-13]	12.7[11.2-14.4]
Reticulocyte count (g/l), med [IQR]	50[37-74]	78[62-110]	78[58-104]
Total bilirubin , med [IQR]	3.75[3-6.45]	5.3 [4-9]	7 [5-10]
LDH (UI/ml), med [IQR]	338[276-392]	327[233-434]	200[170-250]
Haptoglobin (g/l), med [IQR]	1.19[0.41-1.9]	0.85[0.56-1.45]	0.47[0.1-1]
% Hémoglobine S, med [IQR]			
In AS donor (N=18)	28 % [27-31]	38 % [32-38]	39% [34-40]
In AA donor (N=3)	0	0	0
Donor chimerism (%)			
≥ 95%	100%	85,9%	85,9%
50-95%	0	9,4%	4,7%
20-50%	0	0	4,7%
5-20%	0	0	0
<5%	0	4,7%	4,7%

med: median. IQR: interquartile. LDH: lactate desydrogenase.

Table 3: Quality of life

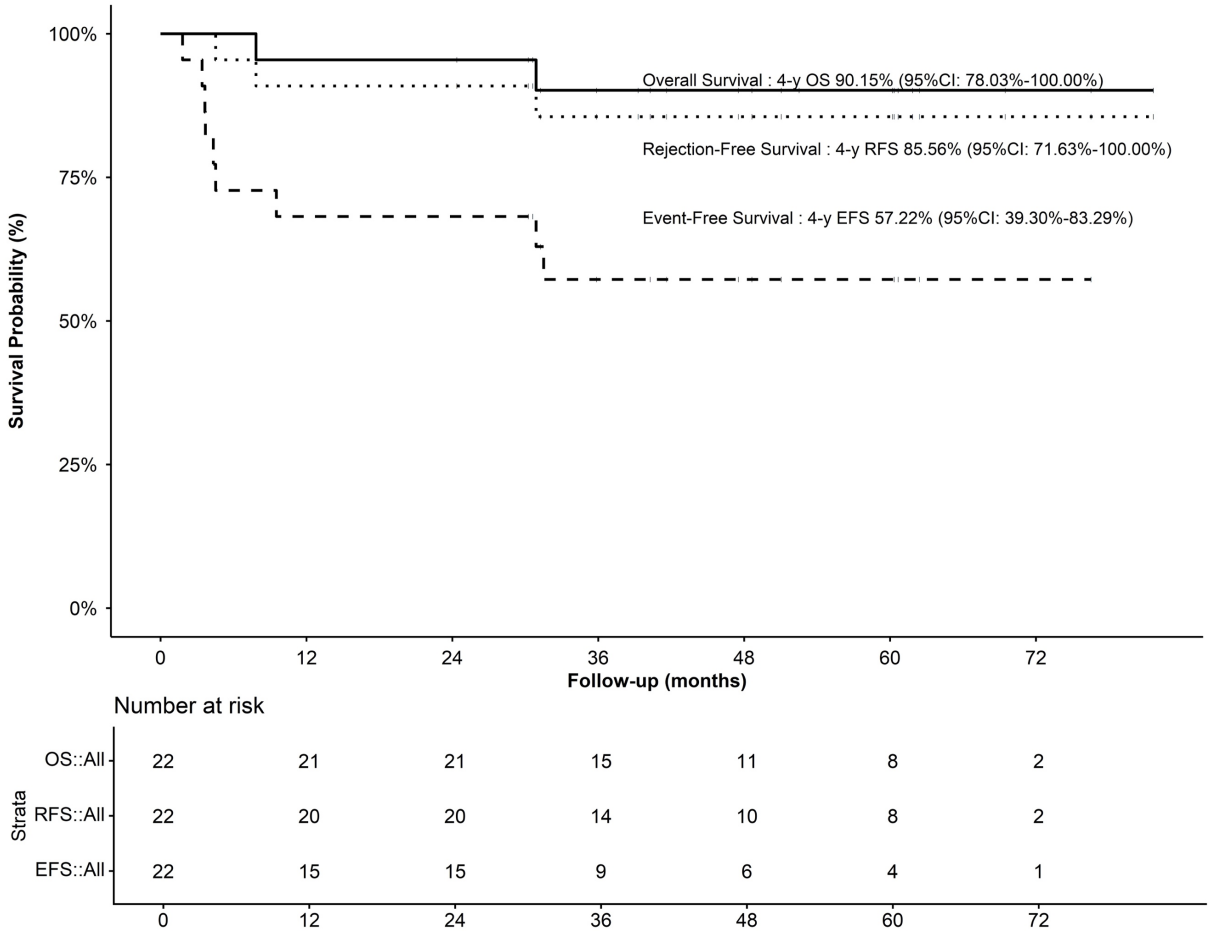
In adolescents (N=14 at transplant) according to the PedsQL 4.0 self-report	Physical score	Emotioning score	Social score	School score	Total score
Pre-transplant N=9 (64%)					
median[IQR]	48.44 [43.75, 56.25]	65[60, 70]	72.5 [63.75, 85]	52.5 [36.25, 57.92]	55.98 [48.8, 62.8]
M3 N=10 (71%)					
median[IQR]	59.38 [56.25, 84.38]	75 [55, 93.75]	80[65, 100]	55[40, 75]	66.30 [48.9, 85.9]
M6 : N=10 (71%)					
median[IQR]	62.50 [59.38, 84.38]	60[50, 75]	85 [70, 100]	62.50 [43.7, 76.25]	66.30 [51.1, 81.2]
M12 N=6 (43%)					
median[IQR]	71.88 [62.50, 78.12]	65 [55, 85]	90 [90, 95]	55[55, 56.25]	65.22 [64.1, 77.2]
M24 : N=3 (21%)					
median[IQR]	90.62 [85.94, 95.31]	90 [85, 95]	95[92.50, 97.50]	72.5 [63.75, 81.25]	87.5[82.3, 92.6]

In adults (N=8 at transplant) according to the EORTC QLQ-C30 self-report	Physical score	Emotioning score	Social score	Fatigue	Pains	Total score
Pre-transplant N=8 (100%)						
median[IQR]	88.9 [77.7, 91.6]	66.7 [58.3, 91.7]	100 [66.7, 100]	66.7 [47.2, 77.8]	58.3 [29.7, 83.3]	58.3 [54.2, 66.7]
M3 : N=6 (75%)						
median[IQR]	83.3 [69.4, 97.2]	58.3 [50.0, 79.1]	100[87.5, 100]	38.9 [33.3, 52.8]	50.0 [12.5, 62.5]	62.5 [52.1, 79.2]
M6 : N=8 (100%)						
median[IQR]	88.9 [77.8, 88.9]	83.3 [66.7, 83.3]	83.3 [83.3, 100]	66.7 [55.5, 66.7]	66.7 [66.7, 83.3]	66.7 [64.6,77.1]
M12 : N=9 (100%)						
median[IQR]	94.4 [80.5, 100]	83.3 [70.8, 95.8]	66.7 [54.2, 91.7]	61.1 [36.1, 86.1]	66.7 [54.2,79.2]	66.7 [54.2, 79.2]
M24 : N=9 (100%)						
median[IQR]	94.4 [88.9, 100]	100[87.5, 100]	83.3 [70.8, 83.3]	66.7 [50, 75]	66.7 [54.2, 79.2]	70.8[54.2, 81.2]

IQR : interquartile. M : months post-transplant. One adult who died 8 months post-transplant was not evaluable at 12 and 24 months.

Two adolescents who turned 18 during follow-up initially completed the pediatric self-report and subsequently switched to the adult version.

Figure 1: Post-transplant outcomes. Event free survival was defined by survival without rejection and without moderate to severe chronic graft versus host disease.



Supplementary data.

Methods *:*

- *Inclusion criteria*. Patients were required to have at least one severe SCD-related complication including: cerebral vasculopathy with arterial stenosis with abnormal magnetic resonance angiogram (MRA) despite extended transfusion therapy; history of acute chest syndrome (ACS) or vaso-occlusive crises (VOCs) despite hydroxyurea therapy pulmonary hypertension (mean pulmonary artery pressure >25 mmHg, by right heart catheterization); tricuspid regurgitant velocity ≥2.5 m/s with left ventricular ejection fraction (LVEF) <55%; severe transfusion difficulties or alloimmunization; renal damage (albuminuria/creatininuria ratio >30 mg/mmol), or estimated creatinine clearance <80 mL/min/1.73m²); history of acute hepatic sequestration with hepatic failure; need for chronic red blood cell (RBC) transfusions during at least one year.
- *Exclusion criteria*. Patients with the following criteria were excluded: ECOG performance status >1, forced expiratory volume and forced vital capacity <50%, NYHA class ≥2 pulmonary hypertension, conjugated bilirubin >50 µmol/L, creatinine clearance <30 mL/min/1.73m², LVEF <45%, anti-HLA donor-specific antibodies (DSA), active human immunodeficiency virus infection, uncontrolled severe infections, pregnancy or lactation, legal incapacity.
- *Pre-Transplant recipient management*. Patients received red cell transfusions or erythrapheresis to maintain hemoglobine S(HbS) levels below 30% during the three months preceding transplant. Chelation therapy aimed a hepatic iron concentration (MRI-based) below 10 mg/g liver tissue and cardiac T2* MRI values above 12 milliseconds, before transplant. For patients with poorly controlled pain, a specialized pain consultation was conducted pre-transplant: optimization of analgesia was prioritized to ensure clinical stability during hospitalization. For male patients, sperm cryopreservation was recommended prior to hydroxyurea initiation. Female patients were referred to reproductive biology consultation and offered ovarian tissue or oovocyte cryopreservation. In patients with a history of alloimmunization or delayed hemolytic transfusion reactions, preemptive immunosuppressive

treatment and secure availability of compatible red blood cell units were required before proceeding.

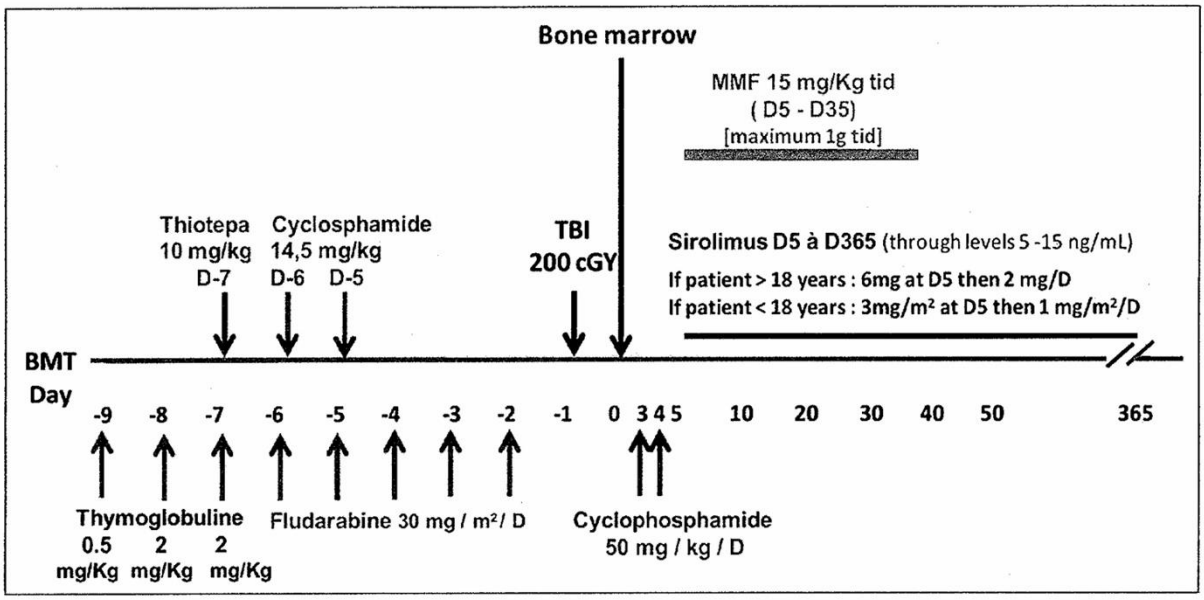
- Definitions : Neutrophil recovery was defined as three consecutive days with neutrophil count above 0.5 x 10^9/L; platelet recovery as three consecutive days with platelet count above 50 x 10^9/L. Acute GVHD (aGVHD) and cGVHD were defined and staged as previously reported.[1,2]

1. Przepiorka D, Weisdorf D, Martin P, et al. 1994 consensus conference on acute GVHD grading. Bone Marrow Transplant. 1995; 15(6):825-828.

2. Vigorito AC, Campregher PV, Storer BE, et al. Evaluation of NIH consensus criteria for classification of late acute and chronic GVHD. Blood. 2009;114(3):702-708.

Results:

- **Supplemental Figure 1:** Transplant modalities. D : day. BMT bone marrow transplantation. TBI : total body irradiation.tib : three times in a day. MMF : mycophenolate mofetil.



➢ Supplemental Table 1

Table 1 : Infections grade 2-5 during the first 24 months post-transplant	Number (%)
Total episodes	85 (100)
Severity	# episodes (%)
- Grade 2	51 (60)
- Grade 3	32 (37.6)
- Grade 4	2 (2.3)
- Grade 5	0
Number of episodes by patient	# patients (%)
- 0	1 (4.5)
- 1	4 (18.1)
- 2	3 (13.6)
- 3	3 (13.6)
-> 4	10 (45.4)
Infection timing	# episodes (%)
- Before day 30	36 (42.3)
- From day 30 to day 100	33 (38.8)
- After day 100	15 (17.6)
- Missing data	1 (1.1)
Infection and GVHD	
(acute grade II-IV or chronic moderate to severe)	# episodes
- Episodes number in 10 pts with GVHD : median (range)	4 (0-7)
- Episodes number in 12 pts without GVHD: median (range)	3 (1-9)
Infection site	# episodes (%)
- Bacteremia or severe sepsis/ fungemia	29 (34.1)
- Pneumonitis	5 (5.8)
-Urinary tract infection [BK virus cystitis]	10 (11.6) [4]
-Ear, nose, and throat infection	4 (4.7)
-Gastrointestinal tract	5 (5.8)
-Osteomyelitis	1 (1.1)
- Viral replication without clinical disease	20 (23.5)*
- No documented infection site	11 (12.9)
Pathogen type	# episodes (%)
-*Bacterial*	**38 (44.7)**
• Pseudomonas aeruginosa	6
• Escherichia coli	5
• Other Gram-negative bacilli	11
• Staphylococcus aureus	6
• Streptococcus pneumoniae	1
• Clostridium difficile	2
• Other bacteria	7
– *Viral*	**29 (34.1)**
• Cytomegalovirus (CMV)	8
• Epstein-Barr virus (EBV)	4
• BK virus	4
• Adenovirus	2
• SARS-CoV-2	1
• HSV/VZV	5
• HHV-6	5
– *Fungal*	**4 (4.7)**
• Pneumocystis jirovecii	1
• Geotrichum capitatum	1
• Candida spp.	2
-*Non-microbiologically documented infections*	**14 (16.5)**

: number. HSV: herpes simplex virus. VZV: varicella zoster virus
SARS-CoV-2: severe acute respiratory syndrome coronavirus2.
* related to CMV (n=8), EBV (n=4), HHV-6 (n=5), adenovirus (n=2), SARS-CoV-2(n=1).