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# Allogeneic hematopoietic stem cell transplantation in patients with sickle cell disease with alternative donors – Case series

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## ABSTRACT

Sickle cell disease is a hereditary hemoglobinopathy characterized by the presence of hemoglobin S (HbS), which leads to erythrocyte deformation, promotes hemolysis, and causes recurrent vaso-occlusive crises with multisystem involvement. Therapeutic options include pharmacological agents such as hydroxyurea, chronic blood transfusions, and, in selected cases, allogeneic hematopoietic stem cell transplantation (allo-HSCT), which remains the only curative option currently available. Here, we describe four cases that underwent allo-HSCT due to severe disease-related complications, highlighting the effectiveness of the procedure in appropriately selected cases.

**Keywords:** Sickle cell disease; Allogeneic transplant; Graft-versus-host disease (GVHD); Hemoglobinopathy.

## INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive genetic disease caused by a mutation in the beta-globin gene, resulting in the production of hemoglobin S (HbS).[1] The polymerization of this abnormal hemoglobin under hypoxic conditions causes deformation of erythrocytes into a sickle shape, increasing their fragility and favoring vaso-occlusive crises, with progressive tissue damage.[2] Globally, the prevalence of SCD varies significantly, being more frequent in populations of African, Mediterranean, and Indian subcontinent origin.[2,3] Its impact on the quality of life of patients is considerable due to complications such as recurrent painful crises, progressive organ damage, and an increased risk of thrombotic events.[2-4] The life expectancy among patients with SCD is reduced to 52.6 years, according to a study conducted in the United States.[5] In Latin America, data from Brazil indicate that life expectancy and mortality estimates for patients with SCD reveal a median age at death of 32 years, compared with 69 years in the general population.[6]

In addition to the homozygous form (HbSS), the disease can occur in heterozygous individuals who carry combinations of HbS with other hemoglobinopathies, such as double heterozygosity with hemoglobin C (HbSC), hemoglobin E (HbSE), or β-thalassemia (HbS/β-thalassemia), among others. These variants can manifest with clinical phenotypes of variable severity, from mild forms to clinical pictures with complications similar to classical sickle cell anemia.[2,4-7]

Therapeutic management includes the use of drugs such as hydroxyurea, which increases fetal hemoglobin production and reduces the incidence of vaso-occlusive crises.[8] However, in patients with severe manifestations, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative option available. This procedure is highly effective in preventing long-term complications and improving disease-free survival (DFS) and quality of life in patients with SCD.[9-11] Transplants performed with HLA-matched sibling donors (MSD) have shown favorable success rates, with a low incidence of graft rejection and graft-versus-host disease (GVHD).[11,12]

Various strategies have been implemented to optimize the outcomes of allo-HSCT, extend its use to patients without MSD, and reduce the toxicity of conditioning. The Johns Hopkins group described a nonmyeloablative conditioning regimen for HLA-haploidentical transplantation based on fludarabine (150 mg/m$^2$), cyclophosphamide (29 mg/kg), total body irradiation (2 Gy or 4 Gy), and thymoglobulin (4.5 mg/kg), incorporating post-transplant cyclophosphamide (PT-Cy) (50 mg/kg/day on days +3 and +4) for GVHD prophylaxis.[13-15] This platform decreases the recipient's immunoburden, facilitates graft acceptance, and reduces the incidence of rejection, while minimizing the adverse effects associated with conventional conditioning regimens.[13-15] Anurathapan et al.[16] also used two cycles of lymphodepletion with fludarabine and dexamethasone before the start of conditioning to improve engraftment in patients who underwent transplantation for B-thalassemia in the setting of mismatched donor transplantation. Sirolimus was used to reduce the neurological toxicity associated with calcineurin inhibitors in these patients.[17] In addition, sirolimus plays a role in inducing immunotolerance in patients with SCD.[13]

We describe a case series of patients with SCD without MSD who underwent allo-HSCT using alternative donors, nonmyeloablative conditioning, and prior lymphodepletion, and analyze their clinical course and associated complications.

Regarding ethical aspects, we report that the study was conducted as a retrospective analysis using previously collected clinical data. Strict patient confidentiality was maintained in accordance with the principles of the Declaration of Helsinki. Due to the study's retrospective nature, informed consent from individuals was not required. This work was approved by the Institutional Health Research Ethics Committee of the Private Hospital – Medical Center of Córdoba S.A. (Ref HP 4-388).

## Clinical cases

### Case 1

A 10-year-old male with homozygous SCD (S/S) was diagnosed at 2 years of age. Oculocutaneous albinism was also identified, along with a family history of heterozygous HbS carriers in the mother. Before allo-HSCT, the patient was receiving treatment with folic acid, deferasirox, and amoxicillin prophylaxis. Preparation with hydroxyurea and periodic erythrocytapheresis was initiated due to his high transfusion requirements (every 21 days), hemolytic crises with liver abnormalities, and iron overload.

Allogeneic HSCT was performed with a 9/10 B-leader-matched, double permissive DPB1-mismatched unrelated donor, following nonmyeloablative conditioning.[15] Before transplant, he underwent two cycles of lymphodepletion.[16] GVHD prophylaxis included PT-Cy, sirolimus, and mycophenolate (Table 1).

During the first 100 days post-allo-HSCT, the patient developed febrile neutropenia without germ isolation, grade 3 oropharyngeal mucositis, and engraftment syndrome. Additionally, he presented cytomegalovirus (CMV) reactivation and intestinal giardiasis, which resolved with specific treatment. A grade II acute cutaneous GVHD was diagnosed, confirmed by skin biopsy, which responded favorably to corticosteroid therapy. Later, on day +350 post-transplant, after a respiratory rhinovirus infection, the patient was diagnosed with chronic GVHD with moderate pulmonary involvement, for which he began FAM therapy (fluticasone, azithromycin, and montelukast) along with immunosuppression with sirolimus. Ruxolitinib was subsequently added, resolving the condition completely.

**Table 1.** Clinical and transplant characteristics of the four patients undergoing HSCT in Argentina.

| Variable | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| Age at transplant | 10 years | 25 years | 24 years | 30 years |
| Patient sex | Male | Male | Female | Male |
| Personal pathological history | Homozygous S/S, oculocutaneous albinism | Homozygous S/S, splenectomy. cholecystectomy, mononucleosis, pneumonia | Double heterozygous HbS/beta thalassemia. Previous bone marrow transplant with loss of chimera. Bilateral hip replacement. Alloantibody sensitization (hemolytic crisis). | Double heterozygous HbS/beta thalassemia. Splenectomy. Osteonecrosis of both hips. |
| Indication of transplantation | Frequent transfusion requirements with iron overload | Poor control of HSCT with ischemic attacks (bone, stroke, liver) and DVT despite splenectomy, hydroxyurea, and erythrocytapheresis | Poor control with hemolytic crisis, iron overload, and altered liver function tests. Sensitization with alloantibodies. | Pain crisis, difficult treatment management. Iron overload. |
| Type of transplantation | Mismatched unrelated donor; 9/10 (B leader peptide matched) | Haploidentical related, heterozygous HbS carrier, negative DSA | Matched unrelated donor (DP permissive mismatch) | Haplocord-related. Negative DSA. |
| Functional status | Lansky 100% | ECOG: 2 | Karnofsky: 90%/ECOG: 1 | Karnofsky: 90%/ECOG: 1 |
| HCT-CI | 3 points. Increased transaminases | 5 points. Elevated bilirubin and increased transaminases. Ischemic stroke. | 1 point. Increased transaminases. | 1 point. Psychiatric disorder |
| Recipient/donor blood type | B positive/B positive | O positive/O positive | O positive/O positive | A positive/O positive |
| Recipient/donor CMV serology | Positive/positive | Positive/positive | Positive/negative | Positive/positive |
| Donor age | 25 years | 13 years | 24 years | 50 years |
| Donor gender | Female | Male | Male | Female |
| Source of stem cells | Peripheral blood | Peripheral blood | Peripheral blood | Peripheral blood |
| Product cellularity | CD34+: $6.4 \times 10^6$/Kg/CMN: $17.2 \times 10^8$/Kg/CD3+ 6.9 x $10^8$/kg | CD34+ $12.2 \times 10^6$/kg/$10.9 \times 10^8$/Kg/CD3+ $1.8 \times 10^6$/kg | CD34+ $9.9 \times 10^6$/kg/$11.8 \times 10^8$/Kg/CD3+ $2.8 \times 10^6$/kg | CD34+ $10.3 \times 10^6$/kg/$7.87 \times 10^8$/Kg/CD3+ $2.8 \times 10^6$/kg |
| Neutrophil engraftment (> 500/uL) | 15 days post-transplant | 28 days post-transplant | 14 days post-transplant | 24 days post-transplant |
| Platelet engraftment (> 20.000/uL) | 21 days post-transplant | 28 days post-transplant | 11 days post-transplant | 25 days post-transplant |
| Early complications (< 100 days post-transplant) | Febrile neutropenia without germ isolation, grade 3 oropharyngeal mucositis, engraftment syndrome, CMV reactivation, intestinal giardiasis. GVHD with cutaneous involvement, MAGIC II, International Bone Marrow Transplant Registry C. | Grade III intestinal and cutaneous GVHD. Alloantibody hemolysis. CMV reactivation. | Grade III cutaneous GVHD and liver function abnormalities. CMV reactivation, | Cutaneous and hepatic GVHD MAGIC grade III B. CMV reactivation. BK cystitis. |
| Late complications (> 100 days post-transplant) | Respiratory rhinovirus infection, FEV1 decline, with a restrictive pattern. *Hemophilus influenzae*. Chronic lung GVHD, National Cancer Institute consensus score II 2014. | Medullary decompression of the talus, cuboid, calcaneus, scaphoid, and humerus. Osteonecrosis of the hip, knee, talus, and multiple bone infarcts. Urethral stricture. | Continue with hormone replacement therapy. | Liver GVHD. Whipple's disease. Epstein-Barr virus reactivation. Recurrent infections (otitis, sinusitis, bronchitis) due to hypogammaglobulinemia. *Pneumocystis carinii* pneumonia. |

ECOG: Eastern Cooperative Oncology Group; HCT-CI: hematopoietic cell transplantation-comorbidity index; MAGIC: Mount Sinai Acute GvHD International Consortium. Source: Elaborated by the authors.

Chimerism monitoring showed 100% at all follow-up visits, with no HbS detected. Currently, at 20 months (600 days) post-transplant, his liver enzymes and bilirubin are close to normal, his general condition is satisfactory (Lansky 100%), and SCD-related post-transplant complications have not recurred.

**Case 2**

A 25-year-old male was diagnosed with homozygous SCD (S/S) at 3 years of age. Since childhood, he had experienced multiple complications, including splenectomy at age 10, recurrent pneumonia, deep vein thrombosis (DVT), bone ischemic attacks, and cerebrovascular events. His pretransplant management included transfusions every 14-21 days, erythrocytapheresis, hydroxyurea, and chelation therapy due to significant iron overload.

A haploidentical allo-HSCT was performed with his brother, a heterozygous carrier of Hb S, as the donor (Table 1). No donor-specific antibodies (DSA) were detected. The conditioning was non-myeloablative1,[15] and one course of pre-transplant lymphodepletion was indicated.[16] PT-Cy, sirolimus, and mycophenolate were administered as prophylaxis for GVHD.

The patient developed grade III acute intestinal and cutaneous GVHD, which was resolved with corticosteroid therapy and infliximab. He also presented with hemolytic anemia requiring treatment with rituximab. No chronic GVHD was recorded.

After transplantation, the patient showed stable HbS levels consistent with a heterozygous HbS pattern (40%). He has maintained donor chimerism above 95%, and liver enzymes and haptoglobin have normalized. Immunosuppression was discontinued 970 days after transplantation. Currently, more than 7 years (2,700 days) post-transplant, he continues to require analgesics and physical therapy due to ischemic episodes that resulted in irreversible bone damage.

**Case 3**

A 24-year-old woman was diagnosed at 4 months of age with SCD, double heterozygous HbS/beta-thalassemia. She presented with frequent hemolytic crises, iron overload, and recurrent painful crises. At 4 years of age, she underwent an MSD transplantation from her sister, a heterozygous beta-thalassemia carrier, which resulted in complete secondary loss of chimerism and autologous reconstitution. Her medical history included splenectomy at 10 years of age, a severe hemolytic crisis due to warm antibodies with a risk of death that was refractory to corticosteroids and required treatment with intravenous immunoglobulin, and bilateral hip osteonecrosis with progressive functional limitation. In addition, she developed anti-HLA class I and II antibodies with a mean fluorescence intensity (MFI) ranging from 5,000 to 20,000.

Allo-HSCT was performed using an HLA-matched unrelated donor 20 years after the first transplant (Table 1). She underwent nonmyeloablative conditioning[15] and two cycles of lymphodepletion prior to transplantation.[16] GVHD prophylaxis was provided with PT-Cy, sirolimus, and mycophenolate.

The patient presented with grade III acute cutaneous GVHD and transient liver damage, which was treated with corticosteroid therapy and resolved completely. Hypogonadism was also registered, requiring hormone replacement therapy.

After transplantation, she exhibited HbS levels of 0% beginning 180 days post-transplant. She has maintained 100% donor chimerism and discontinued immunosuppression after 2 years. At 6 years (2,190 days) post-transplant, she has a Karnofsky performance status of 100%, with no hemolytic crises.

**Case 4**

A 30-year-old male was diagnosed with double heterozygous SCD (HbS and beta-thalassemia) during the first months of life. His clinical course included multiple hospitalizations for painful crises, liver involvement,

and severe bone complications. He required transfusions every 3-4 months and had a history of recurrent vaso-occlusive crises and progressive bone marrow infarction. In addition, he developed anti-HLA class I antibodies with an MFI ranging from 2,000 to 10,000.

A haploidentical allo-HSCT was performed with his mother as the donor (Table 1). No DSA was found against this donor. Non-myeloablative conditioning and two courses of lymphodepletion prior to transplantation were administered.[15,16] For GVHD prophylaxis, he received PT-Cy, sirolimus, and mycophenolate mofetil.

The patient developed grade III acute hepatic GVHD, which was refractory to corticosteroids and required treatment with photopheresis and ruxolitinib. He also presented with Whipple's disease and Epstein-Barr virus reactivation, which were managed with antibiotics and rituximab, respectively. In addition, developed secondary immunodeficiency with recurrent infections, requiring monthly immunoglobulin therapy. No chronic GVHD was recorded.

After transplantation, his HbS level was 0% at 180 days post-transplant. He achieved complete donor chimerism. He is now more than 4 years (1,700 days) post-transplant, with progressive improvement in his nutritional status. Immunosuppressive treatment was discontinued 820 days post-transplant.

## DISCUSSION

We present four patients with SCD who lacked an MSD and underwent transplantation from alternative donors, using the same nonmyeloablative conditioning regimen and GVHD prophylaxis, with prior lymphodepletion to reduce the risk of graft failure. Allo-HSCT in patients with SCD is a curative option that is increasingly available due to the use of alternative donors, enabling the eradication of sickle cell hematopoiesis and disease-related complications.[8] However, its implementation is associated with complications, including graft failure, opportunistic infections, conditioning-related toxicity, and GVHD.[18] To determine the risks and benefits of transplantation, it is important to understand the expected mortality rate in patients with SCD, which depends on age and the severity of clinical manifestations. In a contemporary cohort of adults with HSCT in the United States, the mortality incidence rates were 2.36 (95%CI 1.57-3.42) and 4.72 (95%CI 2.70-7.67) deaths per 100 person-years among individuals aged 18 to 36 years and older than 36 years, respectively.[19] The decision to pursue allogeneic HSCT should be individualized, and the risk-benefit ratio should always be carefully considered. Although indications have broadened over time, stroke, acute chest syndrome, and recurrent vaso-occlusive crises remain the most common indications.[20] A meta-analysis of allo-HSCT outcomes in SCD, including 2,853 pediatric and adult patients, reported an overall survival (OS) rate of 96%, DFS of 90%, acute GVHD in 20% of patients, chronic GVHD in 10%, and non-relapse mortality of 4%, demonstrating that allo-HSCT is a safe and effective therapy with OS exceeding 90%. The graft failure rate was higher in adults than in pediatric patients (14% vs. 5%). It is important to note that most patients in this study underwent transplantation with an MSD, followed by haploidentical transplants, and lastly, transplants from unrelated donors.[21]

In our series, three of the four patients were adults (25, 24, and 30 years old) at the time of transplantation. Adult patients are characterized by more severe phenotypes, and there are fewer reported data on allo-HSCT in this age group.[22,23] However, the use of reduced-intensity or nonmyeloablative conditioning has achieved favorable outcomes exceeding 90% in the patient population.[24] In our cohort, a high success rate was observed in terms of hematopoietic engraftment, absence of detectable HbS, and discontinuation of transfusion dependence. There were no deaths in our cohort. However, GVHD was a frequent complication, highlighting the importance of immunosuppressive prophylaxis and post-transplant monitoring.[25] All patients received peripheral blood as the stem cell source, which is associated with a higher incidence of chronic GVHD.[26] This factor, together with the fact that three of the four patients received a $CD34^+$ cell dose of at least $10 \times 10^6$/kg, may have contributed to the incidence of GVHD.[27] Furthermore, all four patients received sirolimus as previously recommended. The use of sirolimus in the context of PT-Cy is associated with a lower rate of neurological complications as well as a reduced incidence of GVHD.[28,29] New strategies, such as the use of abatacept, may further reduce the incidence of GVHD in allo-HSCT.[30]

Graft failure is another potential complication; in fact, in our series, patient 3 underwent allo-HSCT in childhood with an MSD and experienced secondary graft failure. Pre-transplant immunosuppression strategies, such as lymphodepletion[16,31] or the use of azathioprine and hydroxyurea,[32] have been used to improve chimerism levels and reduce the post-transplant graft failure rate; additional strategies are currently being explored, including the incorporation of thiotepa into conditioning regimens.[33] None of our patients had donor-specific antibodies, another known factor associated with an increased risk of graft failure in the setting of HLA-mismatched donor transplantation.[34,35] Patient 2 underwent transplantation with a family donor who was an HbS carrier. Individuals with sickle cell trait, those carrying a single mutated allele and who are asymptomatic, have traditionally been considered acceptable donors, without adversely affecting overall transplant outcomes.[36]

All four cases presented here maintained immunosuppression for at least 1 year after transplantation. Prolonged immunosuppression increases the risk of serious viral and bacterial infections, as evidenced in these cases by CMV and Epstein-Barr reactivations.[25,37] This underscores the need for rigorous surveillance and effective antimicrobial prophylaxis to reduce post-transplant morbidity.[25,37,38] Musculoskeletal complications, such as osteonecrosis and orthopedic sequelae, also represent a major challenge in these patients. Physical rehabilitation, pain management, and bisphosphonate therapy to optimize bone density may be key to improving mobility and quality of life.[39] Overall, HSCT has been shown to improve quality of life by reducing painful crises and recurrent hospitalizations, although some long-term sequelae persist.[9] Appropriate donor selection and conditioning regimens remain crucial to minimizing adverse effects and optimizing clinical outcomes.[12]

The implementation of HSCT faces significant barriers, particularly in low- and middle-income countries. The limited availability of compatible donors, especially HLA-identical donors, and the absence of unrelated donor registries in many regions present a major challenge.[40] Furthermore, the medical infrastructure required to safely perform transplants, including specialized units and trained personnel, remains inadequate in much of sub-Saharan Africa and other regions with a high prevalence of SCD.[41] Encouraging outcomes using both MSD and alternative donors have been reported from Brazil in both private and public centers.[42-44] The cost of the procedure constitutes another critical barrier. Although innovative approaches have been implemented in some countries, such as Egypt and India, HSCT remains inaccessible to most patients. The risks associated with HSCT, including GVHD and procedure-related mortality, together with a lack of education and awareness of this therapy, also contribute to its low uptake.[42]

Finally, although HSCT remains the only curative treatment available for sickle cell anemia, the development of new therapeutic strategies, such as gene therapy, may offer alternative options with lower toxicity.[45] However, these approaches remain extremely expensive, are not widely accessible, and may not achieve a 100% success rate.

## CONCLUSION

Allo-HSCT represents a viable curative strategy for patients with SCD and severe complications. However, optimizing conditioning protocols, carefully selecting donors, and ensuring early management of post-transplant complications are essential to improving clinical outcomes and quality of life for transplant recipients.

## CONFLICTS OF INTEREST

Nothing to declare.

## DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

During the preparation of this work, the author(s) used Copilot chat to correct grammar. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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## DATA AVAILABILITY STATEMENT

All data were generated or analyzed in this study.

## AUTHOR CONTRIBUTIONS

**Conceptualization:** Basquiera AL, Arbelbide JA, Orozco ML, Ferini GA, Mas ME, Sepich MM. **Investigation:** Basquiera AL, Arbelbide JA, Ferini GA, Mas ME, Sepich MM. **Methodology:** Basquiera AL, Arbelbide JA, Sepich MM. **Formal Analysis:** Basquiera AL, Sepich MM. **Data Curation:** Basquiera AL, Sepich MM. **Project Administration:** Basquiera AL, Sepich MM. **Writing:** Sepich MM. Milanesio M. **Supervision:** Mas ME, Basquiera AL. **Final Approval:** Basquiera AL.

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