

Hematopoietic stem cell transplant therapy, clinical trials, complications, and quality of life for patients with Sickle cell anemia: Clinical potential and future perspectives

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Abstract

Background: Sickle cell anemia (SCA) is an inherited monogenic disorder. The clinical symptoms of SCA are protean, including vaso-occlusion, hemolysis, early stroke, leg ulcers, multi-organ failure, and increased risk of premature death. Hematopoietic stem cell transplantation is the only treatment identified to reduce SCA-related organ damage. Unfortunately, graft rejection is a significant impediment to these strategies.

Materials and Methods: The current standard of treatment for the past two decades is limited to myeloablative-matched sibling donors, which is likely to be only for minor patients and is feasible for non-malignant giant disease. Cumulative studies showed that HSCT increases overall survival and quality of life in patients with SCA.

Results: Hematopoietic stem cell transplantation (HSCT) is significantly associated with a higher risk of graft versus host disease and moderate mortality risk. New strategy lacking standard donors includes cord blood, matched unrelated donors/ Haploidentical donors.

Conclusion: This review summarized evidence from HSCT clinical trials from different transplantation methods, specific HSCT and HSCT-related health problems that need to be addressed in medical contexts with patients and family members, and other areas that enhance the quality of life in SCA.

Key words: Hemoglobinopathy, Hematopoietic stem-cell transplantation, Quality of Life, Sickle cell Anemia

Introduction

Sickle cell anemia (SCA) is one of the most widespread and severe hemoglobinopathies among all monogenic inherited diseases. Vaso-occlusive crisis (VOC) is the most common clinical event in SCA; a homozygous condition (HbSS) causes early mortality and severe morbidity due to polymerization of red blood cells (RBCs) and persistent endothelial damage to arteries. It results in significantly reduced life expectancy and unexpected financial burdens (1-3). In some individuals, HbSS may occur combined with other mutations in the

globin gene, such as HbSC disease, alpha thalassemia, and HbSB thalassemia. This mutation is a reflection of the symptoms of patients (4). Over the past several decades, increasing the number of newborn screening (NBS) in an early phase of the child in the United States (US) with supportive care of hydroxyurea (HU) increases HbF levels and significantly reduces pain episodes. In addition, inclusive disease-modifying transfusion therapy reduces the underlying mortality rates (5, 6). A recent cohort study has shown that life expectancy is 54 years of homozygous SCA patients in the US (7).

Currently, there are limited treatment options for SCA management, including nonsteroidal anti-inflammatory drugs (NSAIDs), HU, and blood transfusion therapy. None of these therapeutic strategies is entirely safe. Hematopoietic stem cell transplantation (HSCT) and Gene Therapy (GT) is the only definitive Gold standard curative option for SCA, but GT is still in the early phases of clinical trials. However, HSCT is complex with the risk of transplantation-related mortality (TRM) and expensive but is currently the only well-established treatment for SCA (8). HSCT is a modern treatment and has not achieved widespread acceptance and care among adult SCA patients. Previously, few studies have supported the role of HSCT in adult SCA patients, especially those > 30 years of age (9). Data indicates that SCA children's disease-free survival (DFS) levels were 90 % after a successful HLA-identical sibling HSCT (10). Improved organ function with a significantly reduced risk of SCA-related complications is a vital therapy goal(11). Therefore, HSCT's SCA care is related to the typical Health-related quality of life (HRQOL) spanning mental, physical, and social realms (12). Although HSCT is a promising treatment for SCA, several uncertain issues limit its widespread use, including very aggressive toxic effects such as transplant-related mortality, graft versus host disease (GVHD), graft loss (GL) rates, and difficulties in finding a donor (13). The gross number of HSCT rates for SCA remains much lower than expected due to the high cost of treatment for chronic single-patient transfusions, and chelating alone is \$30,000 per year in the US (14). In this perspective, the price is the main factor behind the disease in low-income countries (15). Overall, the long-term benefits of HSCT have widely accepted SCA treatment. But the number of randomized clinical trials in adult patients is still limited. This detailed review is concentrated on HSCT forms, toxicity, donor selection criteria, patient QOL,

current clinical trials, and HSCT's long-term impact, including other options for enhancing general understanding of SCA care and offering a more realistic approach to patient selection.

Hematopoietic stem cell transplant and Sickle cell disease

HSCT is the only FDA-approved therapy for SCA. Johnson et al. invented the first HSCT for SCA in 1984 (16). It was noted that if patients underwent HU treatment before transplantation, the overall survival and event-free survival rates (EFS) were higher than eight years and 97.4 %, respectively (17). Similarly, for bone marrow and cord blood transplantation (18). HSCT has curative potential for all non-cancer diseases, but it is difficult to define how patients are at higher risk of receiving the procedure. There are several variations in the clinical phenotypes of homozygous SCA patients. It makes it grim to predict the possibility of a successful HSCT procedure. However, some clinical findings may predict transplant-associated complications such as renal insufficiency (RI) at age >16 years, high rates of inflammation, and hepatic abnormalities (19, 20). There is an inherent debate about which SCA patients will go through the treatment. In this circumstance, the decision to treat SCA patients with HSCT was mainly based on the detailed overview of toxic effects and long-term complications in figure 1.

HLA Identical sibling transplantation

Owing to good outcomes from younger donors, SCA Patients with HLA-matched sibling donors (MSD) could be a safer option for transplantation in the early phase of disease progression. The study also strongly indicated that after one year of successful transplantation, there was no more experience of vaso-occlusive crisis (VOC) or organ damage in children (21). If the patient has poor access to the absence of an MSD in support care, consideration must be given to a matched unrelated donor in the presence of severe illness. Recent data shows that 5-year EFS

and OS were 91.4% and 92.9%, respectively, with 23 patients suffering from graft failure and 7% dying from an infection. However, it was reported that the mortality rate was lower in younger patients after HSCT (22). Therefore, professionals commend that indicative patients with an HLA-matched sibling undergo HSCT as early as possible, preferably before school age (23). However, the inconsistency of clinical representation during childhood and the risk of transplantation has been limited in HSCT. In the current situation, this therapy is rarely considered by the hematology and oncology groups due to high toxicity risks. OS and DFS are equal to patients treated with symptomatic disease-free treatment (DMT) in selected patients in (24). A major problem in patients with SCA is seeking sufficient bone marrow transplantation (BMT) or cord blood with an adequate HLA matching degree. Currently, some ongoing clinical trials have remarkably successfully reduced morbidity and mortality associated with HSCT in the case of MSD. A study showed that OS and EFS were 91 % following an HLA-MSD BMT with SCA-free events in Black and non-Black African origin (25). Another study in Atlanta, USA, found that after 4.9 years of follow-up, 24 of the 27 patients survived without clinical symptoms of SCA following treatment with Busulfan and cyclophosphamide before HLA-MSD HSCT (26).

Clinical trials

Trial search outcomes

Seventy-three clinical trials were retrieved from the National Institute of Health (NIH) database. A total of 54 clinical trials of HSCT and SCD were classified as enrolling, completing, or recruiting. In terms of clinical trial phases. Amongst them, 28 trials are in the preliminary experimental phase 1, 26 are in the middle phase (II+III), all trials used single or combined with other drugs such as Alemtuzumab, Cyclophosphamide,

Mycophenolatemofetil, Sirolimus, Fludarabine, ARU-1801, Defibrotide, Rabbit anti-thymocyte globulin, Tacrolimus, Plerixafor, hydroxyurea, azathioprine, alemtuzumab, thiotepa, and CTX001. Above all, most of the trials have cleared ethical approval. The case studies are still in the recruitment phase, whereas some trials have begun recruiting patients. Amongst them, 26 clinical trials are complete in the initial phase and as per the clinical trials database, all studies take next 5 -10 years for precise results (Table I). Several studies have shown that myeloablative transplantation has improved outcomes in young people (less than 16) with MSDs. Multiple regimens have been used, such as Busulfan, and cyclophosphamide, with or without anti-thymocyte globulin (ATG) or anti-lymphocyte globulin, with or without total lymphoid radiation (TLI). Besides, the OS was more than 90%, and the GR was less than 10% had been seen. Immune ablation regimens without myeloablation using combinations of alemtuzumab, HU, FLU, Treosulfan, and Thiotepa had an OS rate of 100 % and an EFS rate of over 90 % (27, 28). Besides, transplants have been less successful in the myeloablative transplantation strategy in older patients with alternative stem cell origin. The Center for International Blood and Marrow Transplant Studies carried out a retrospective study of 67 pediatric patients transplanted between 1989 and 2002, It was observed that in myeloablative condition, the majority of patients were administered busulfan/cyclophosphamide (Bu/Cy) and GVHD prophylaxis with cyclosporine and methotrexate, and DFS and OS were 85% and 97%, respectively (29). Shenoy et al. reported 79 % OS and 69 % EFS at two years in a matched unrelated donor (MUD) HSCT after reduced-intensity conditioning (RIC) with alemtuzumab, fludarabine, and melphalan in children and young adults. However, there were lower survival rates due to GVHD complications (7 out of 8 deaths

due to GVHD) (30). (Detailed clinical data presented in Table II)

HLA matched unrelated/Alternate donor transplantation

The present situation of matched unrelated donor transplantation (MUDT) for SCA is relatively limited. The possibility of finding an HLA MUD is less than desired in SCA patients. On the other hand, previous data suggested that MUD was much less successful than HLA-MSD. A leading study reported in 2011 included 16 patients with SCA for the efficacy of unrelated cord blood transplantation (UCBT) and found that OS and DFS were 94 % and 50 %, while primary grafting failure was the leading cause of treatment failure in 7 patients with SCA(31). Eight severe SCA children enrolled in the Sickle Cell Unrelated Donor Transplant Trial (SCURT) in the United States with alemtuzumab, fludarabine, and melphalan regimens for prophylaxis (GVHD). The cumulative incidence of GVHD was 16 ± 4 percent. One patient died of chronic GVHD and respiratory failure; two patients developed acute GVHD grade II. OS and DFS also found 85 % and 50 %, respectively. The US stopped this trial because of the high rate of grafting rejection (32). These studies suggested that, for a successful UCBT outcome, strict criteria are needed for HLA-typing, regimen intensity, and an ideal minimum dose of cells, which alone are not sufficient to ensure successful treatment.

A report published by the National Marrow Donor Program (NMDP) on 4 million volunteer donors facilitates life-threatening hemoglobinopathy. Approximately 59.7 % of SCA patients will find 6/6 HLA-MUD or UCB majority of patients find at least one HLA-MUD or UCB48. Overall, the HLA-MUDT studies in SCA patients are infrequent and include a small number of patients. It has also been observed that there is an increased risk of graft failure and transplantation-related complications associated with an increased risk of rejection in HLA-MUDT.

However, several possible studies are currently underway to resolve the rate of MUDT rejection at this time.

Health-Related Quality of Life (HRQL) after HSCT

It is well known that SCA patients have a sub-optimal health-related quality of life (HRQL). The manifestations of SCA with psychological (depression and anxiety) and social stress and its complications often affect poor relationships and academic performance. Despite increased acceptance of treatment, HSCT remains the only curative therapy. Recently, the SCA cohort study described improving life expectancy in the US and Brazil, with a projected life expectancy of 54 years for SCA compared to non-SCA patients(7, 33). Many studies related to HSCT in SCA could not suggest the clear benefits of HRQL in patients undergoing HSCT. US-based one-year cohort study using Busulfan, fludarabine, and alemtuzumab regimens confirmed that HRQL might initially decline in the first trimester following HSCT one-year post-HSCT improvement in the overall HRQL score of 16.58 compared with pre-HSCT score 4.45. Besides, clinical manifestations of SCA significantly reduced and improved HRQL (34). 16 out of 26 children who underwent HSCT using the myeloablative conditioning regimen have gone through the Pediatric Quality of Life Inventory (PQLI) and EuroQOL questionnaires. However, score analysis has suggested that HSCT has a positive and encouraging impact on HRQL (35). According to a mixed-method study with Short Form-36, version 1 of the HRQL survey found improvements in healthcare and psychosocial status, and patients were more focused on personal life goals after one year after HSCT (36). The HRQL analysis of 13 SCA children showed a better physical and emotional functioning score after three months of HSCT (37). A retrospective study of 20 SCA patients with Flu / Bu / Cy (Fresenius)/TBI (Fresenius) conditioning regimen found that significant mental and emotional

improvement with SF-36 was observed from the HSCT to the one-year post-HSCT score(38).

Challenges in HSCT for SCA

Following experience with the HSCT procedure in SCA patients, Acute Transplantation complications have remained a significant challenge in SCA patients. In the first clinical trial of HLA-MSD in 1991-1995 for SCA, 32% of children had fatal complications, including central nervous system hemorrhage, acute chest syndrome, lung function abnormality, and cerebral dysfunction. (39). Although the exact etiology is unknown, many SCA patients have pre-existing stroke / silent cerebral infarctions. It could be a threshold for further damage. A study in Belgium, 1998, found that 20 patients had chronic GVHD and post-HSCT acute myeloid leukemia (40). Gaziev et al. have shown Posterior Reversible Encephalopathy Syndrome (PRES) in most children with hemoglobinopathies (41). The research considered the extent of premature ovarian insufficiency (POI) and reduced ovarian reserve (DOR) of young female SCA patients who had been treated with HSCT and HU (42). Cumulative data suggest that SCA children undergoing HSCT have received varying success. In addition, it is needed to consider the molecular mechanisms involved in the neurological disorders typical of SCA patients in clinical trials and research. For the detailed flow of approach for HSCT in SCA is presented in Figure 2.

Clinical questions

Selecting a stem cell transplant procedure and center during a child's SCA treatment can be one of the most critical decisions for the patients and family members. Other than this, some more questions need to be discussed (Figure 3)

Such as;

- What are patients expected to go to HSCT?
- Which donated stem cells are suitable for transplantation?

- What are the benefits of transplanting bone marrow?
- What are the potential short- and long-term risks and the extent of SCA in a single transplant?
- What is the perfect transplant state and timing?
- Different treatment plans for patients based on the availability of donors?
- What are the transplantation and treatment regimens for HSCT?
- How to control or avoid acute HSCT toxicity?

HCT research future direction

Numerous attempts are underway to maximize the exertion of SCD transplants. Currently, only a few established treatments are considered to cure SCD, including hydroxyurea therapy (HUT), chronic transfusion, and the same human leukocyte antigen (HLA) donor in HSCT. HLA-ID HSCT is a full-proof gold standard therapy used to eradicate SCD worldwide. It is essential to centralize HSCT research for step-down toxicity, treatment-related mortality, particularly GVHD, and improving survival. Such work is helpful as a combination therapy. Unfortunately, most patients with first-line bone marrow (BM) deficient in SCD matched the HLA-ID. It is therefore vital that future HSCT work in SCD may explore the use of alternative second-line HSC sources, such as unrelated matched adult donors (URD), unrelated donor umbilical cord blood (UCB), peripheral blood stem cells (PBSC) and associated haploid donors. Therefore, it could be enormous to expand the pool of HSC donors to increase the availability of HSCT to SCD sufferers significantly. This analysis aims to pledge the treatment approach to improve the quality of life of patients with SCD by reducing mortality and morbidity.

Conflict of interest

The authors declare no conflicts of interest.

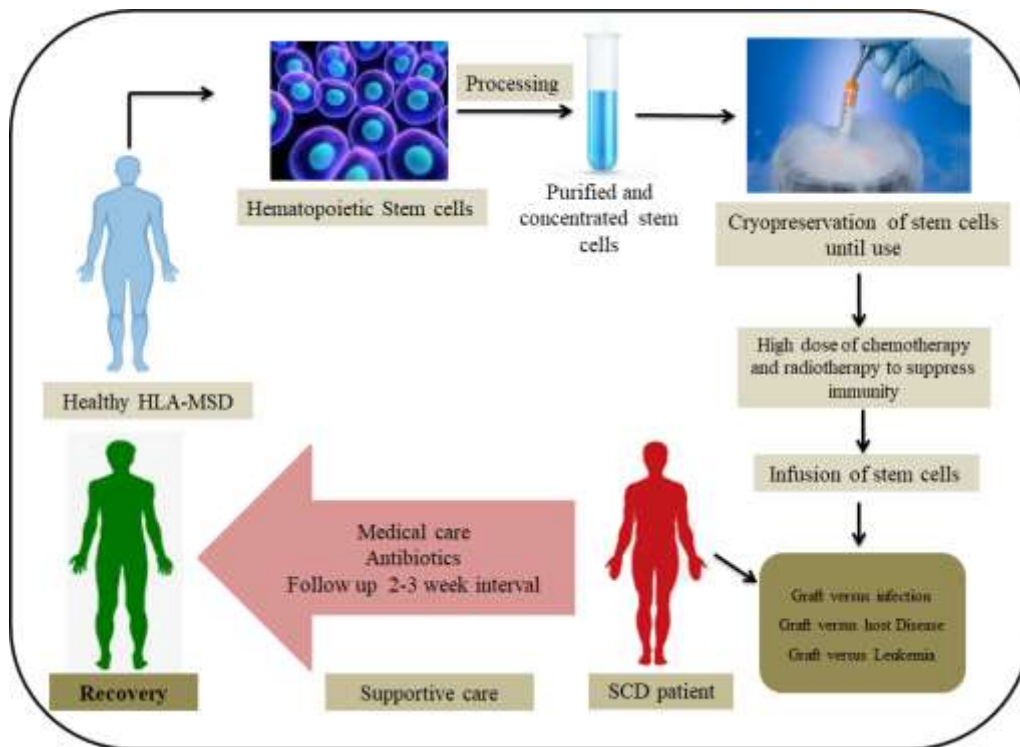


Figure 1. Overview of the HSCT procedure in sickle cell Anemia.

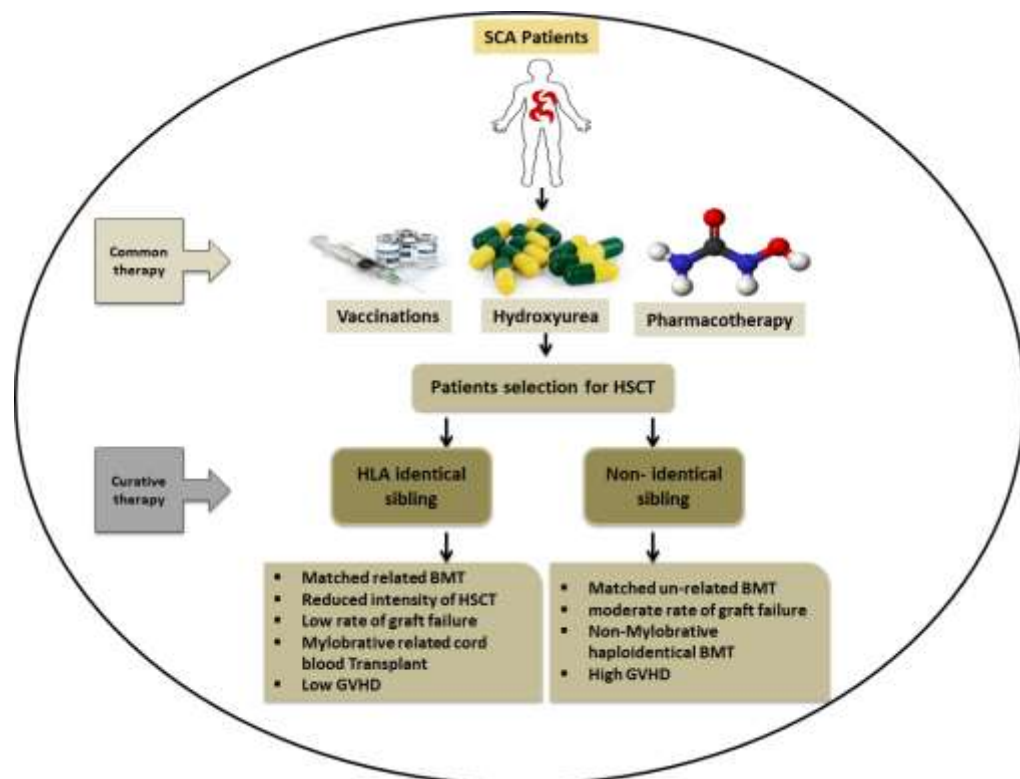


Figure 2. Flow of Approach inpatient's selection of HSCT for SCA

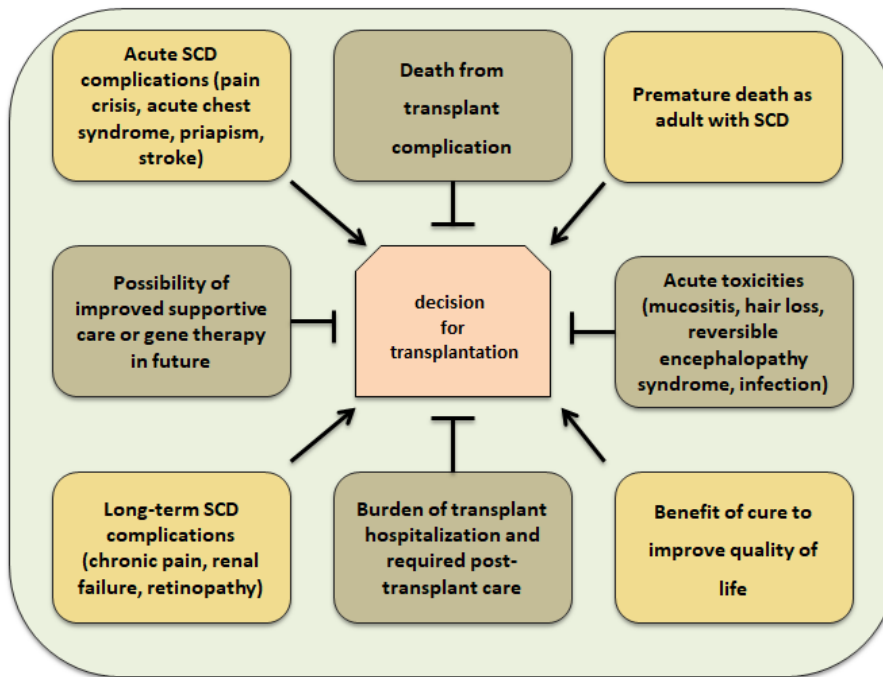


Figure 3: HSCT decision calculus. The final decision to undergo transplantation involves considering several potential risks, benefits, and other variables. A single SCA patient can evaluate each box differently. The figure is modified from (43)

Table I: Summary of different combinational approaches using with HSCT for ongoing clinical trials in the Treatment of Sickle cell disease. PBPC: Peripheral blood hematopoietic progenitor cell, HSCT: Hematopoietic Stem Cell Transplant, BMT: Bone marrow Transplantation, NA: Not Available

| NCT Number | Title | Status | Interventions | Sponsor | Age | Phases | Enrollment | Study Type | Start Date | Completion | Location |
|-------------|---|------------|---|---------------------------------------|----------------------|-----------------|------------|----------------|-------------|------------|---------------------------|
| NCT03279094 | Haploidentical Transplantation With Pre-Transplant Immunosuppressive Therapy for Patients With Sickle Cell Disease | Recruiting | HSCT | City of Hope Medical Center | 1 Year to 30 Years | Phase 1 | 15 | Interventional | 02-Feb-18 | Feb-23 | United States, California |
| NCT00152113 | Haploidentical Stem Cell Transplant for Patients With Sickle Cell Disease and Prior Stroke or Abnormal Transcranial Ultrasound | Completed | HSCT | St. Jude Children's Research Hospital | 2 Years to 16 Years | Phase 1 | 5 | Interventional | Apr-2005 | Dec-2008 | United States |
| NCT04207320 | Haploidentical Hematopoietic Stem Cell Transplantation (HSCT) for Patients With Severe Sickle Cell Disease | Recruiting | $\alpha\beta^+$ T-cell depletion with MiltenyiCliniM ACS system | University of Chicago | 2 Years to 25 Years | NA | 38 | Interventional | Nov-2020 | Nov 2027 | United States |
| NCT00745420 | Evaluating the Safety and Effectiveness of Bone Marrow Transplants in Children With Sickle Cell Disease | Completed | HSCT+ (Alemtuzumab, FludarabineMelfalan) | Medical College of Wisconsin | 3 Years to 19 Years | Phase 2 | 30 | Interventional | Aug-2008 | July 2015 | United States |
| NCT03653247 | A Study to Assess the Safety, Tolerability, and Efficacy of BIVV003 for Autologous Hematopoietic Stem Cell Transplantation in Patients With | Recruiting | Plerixafor, BusulfanBIVV003 | Bioerativa, a Sanofi company | 18 Years to 40 Years | Phase 1 Phase 2 | 8 | Interventional | 28-Jun-2019 | Apr-2023 | United States |

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|--------------------|---|------------|---|--|----------------------|--------------------|----|----------------|-------------|-----------------|---------------|--|
| | Severe Sickle Cell Disease | | | | | | | | | | | |
| NCT02678143 | Nonmyeloablative Conditioning for Mismatched Hematopoietic Stem Cell Transplantation for Severe Sickle Cell Disease | Recruiting | Alemtuzumab,Cyclophosphamide,Mycophenolate mofetil,Sirolimus,Fludarabine | Washington University School of Medicine | 19 years and older | Phase 1 | 20 | Interventional | 26-Apr-16 | October 23-2022 | United States | |
| NCT01499888 | Phase I/II Study of Allogeneic SCT for Clinically Aggressive Sickle Cell Disease (SCD) | Recruiting | Allogeneic Non-Myeloablative Stem Cell Transplantation (Alemtuzumab, Sirolimus) | The University of Illinois at Chicago | 16 Years to 60 Years | Phase 1 Phase 2 | 15 | Interventional | 11-Nov-11 | May-2021 | United States | |
| NCT02065596 | Hematopoietic Stem Cell Transplant for Sickle Cell Disease | Recruiting | Hematopoietic Stem Cell Transplant (HSCT) with Fludarabine | Case Comprehensive Cancer Center | 18 Years to 65 Years | Phase 1 Phase 2 | 25 | Interventional | 24-Apr-2015 | 15-Dec-2020 | United States | |
| NCT03421756 | Stem Cell Transplant in Patients With Severe Sickle Cell Disease | Recruiting | Drug: Alemtuzumab, Sirolimus Radiation: Total Body Irradiation | Kathleen Dorritie | 18 years and older | Early Phase 1 | 12 | Interventional | 29-Mar-2018 | 15-Feb-2022 | United States | |
| NCT04018937 | Early Human Leukocyte Antigen (HLA) Matched Sibling Hematopoietic Stem Cell Transplantation | Recruiting | Fludarabine,Alemtuzumab,Melphalan | Emory University | 2 Years to 10 Years | Phase 2 | 58 | Interventional | 22-Mar-2019 | Jan-2027 | United States | |

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| NCT00186810 | Stem Cell Transplantation With Identical Donors for Patients With Sickle Cell Disease | Completed | Allogeneic stem cell transplant with Busulfan, Cyclophosphamide, Horse ATG | St. Jude Children's Research Hospital | up to 21 Years | Phase 2 | 15 | Interventional | Dec-1992 | Feb-2006 | United States |
| NCT03214354 | Nonmyeloablative Stem Cell Transplant in Children With Sickle Cell Disease and a Major ABO-Incompatible Matched Sibling Donor (Sickle-MAID) | Recruiting | Drug: Alemtuzumab, Sirolimus Radiation: Total Body Irradiation | University of Calgary | 1 Year to 19 Years | Phase 2 | 12 | Interventional | 05-Jul-2017 | Jul-2023 | Canada |
| NCT03121001 | Study of HLA-Haploidentical Stem Cell Transplantation to Treat Clinically Aggressive Sickle Cell Disease | Recruiting | Procedure: Stem cell infusion Drug: ATG, fludarabine, cyclophosphamide, Sirolimus, mycophenolate mofetil Radiation: Total body irradiation | The University of Illinois at Chicago | 16 Years to 60 Years | Phase 2 | 50 | Interventional | 20-Mar-2017 | 12-Sep-2023 | United States |
| NCT04008368 | Repeat Peripheral Blood Stem Cell Transplantation for Patients With Sickle Cell Disease and Falling Donor Myeloid Chimerism Levels | Recruiting | CliniMACS CD34 Reagent | National Heart, Lung, and Blood Institute (NHLBI) | 2 Years to 80 Years | Phase 1 Phase 2 | 30 | Interventional | 24-Oct-2019 | 30-Jan-2024 | United States |

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|--------------------|--|------------|--|--------------------------|----------------------|-----------------|----|----------------|-------------|-------------|---------------|
| NCT03653338 | T-Cell Depleted Alternative Donor Bone Marrow Transplant for Sickle Cell Disease (SCD) and Other Anemias | Recruiting | Biological: CD3/CD19 depleted leukocytes, and CD45RA depleted leukocytes Drug: Hydroxyurea, Rituximab, Alemtuzumab, Fludarabine, Thiotepe | Paul Szabolcs | 5 Years to 40 Years | Phase 1 Phase 2 | 5 | Interventional | 02-Aug-2018 | 01-Aug-2023 | United States |
| NCT02675959 | Myeloablative Conditioning, Prophylactic Defibrotide and HaploAlloSCT for Patients With Sickle Cell Disease (NYMC-571) | Recruiting | Drug: Defibrotide | New York Medical College | 6 Months to 34 Years | Phase 2 | 40 | Interventional | 01-Jul-2017 | Dec-2021 | United States |
| NCT02435901 | HSCT For Patients With High-Risk Hemoglobinopathies Using Reduced Intensity | Completed | Biological: HSCT Drug: alemtuzumab (Campath IH), Fludarabine, Melphalan, Cyclosporine, Mycophenolatem ofetil, Tacrolimus | Northwell Health | 1 Year to 21 Years | Phase 1 Phase 2 | 29 | Interventional | Dec-2008 | Mar-2019 | United States |

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|--------------------|--|------------|---|---|----------------------|---------|----|----------------|-------------|-------------|---------------|
| NCT02225145 | Fertility Preservation in Women Who Will Have Gonadotoxic Therapy or Hematopoietic Stem Cell Transplantation and in Women With Sickle Cell Disease | Completed | NA | Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) | 7 Years to 45 Years | NA | 22 | Observational | 15-Aug-2014 | 09-Sep-2016 | United States |
| NCT01565616 | Bone Marrow Transplantation in Young Adults With Severe Sickle Cell Disease (STRIDE) | Completed | Conditioning Regimen with Bone Marrow Transplant Busulfan (BU), Myleran, BusulfexIV, Fludarabine(FLU), Fludara, Rabbit Anti-thymocyte globulin (ATG), | Emory University | 16 Years to 40 Years | Phase 2 | 22 | Interventional | Mar-2012 | 30-Jun-2016 | United States |
| NCT01340404 | Allogeneic Genoidental Stem Cell Transplantation in Children With Sickle-cell Anemia and Cerebral Vasculopathy (DREPAGREFFE) | Completed | Stem cell transplantation, Transfusion program | Assistance Publique - Hôpitaux de Paris | up to 15 Years | NA | 63 | Interventional | Dec-2010 | Apr-2013 | France |
| NCT00968162 | Sickle Cell Disease Conditioning for Bone Marrow Transplant | Completed | fludarabine | Emory University | up to 18 Years | Phase 1 | 8 | Interventional | Feb-2009 | Mar-2014 | United States |
| NCT02038478 | Allograft for Sickle Cell Disease and Thalassemia | Recruiting | Donor Stem Cell Transplantation | University of Texas Southwestern Medical Center | 18 Years to 45 Years | Phase 2 | 50 | Interventional | Jan-2014 | Jan-2021 | United States |

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|--------------------|---|------------|--|--|----------------------|--------------------|----|----------------|-------------|-------------|---------------|
| NCT04523376 | Pilot Study PBSCT With TCRab Depletion For Hemoglobinopathies | Recruiting | Device: CliniMACS | Children's Hospital of Philadelphia | 2 Years to 25 Years | NA | 20 | Interventional | 14-May-2020 | 01-Jul-2024 | United States |
| NCT03077542 | NonmyeloablativeHaplo identical Peripheral Blood Mobilized Hematopoietic Precursor Cell Transplantation for Sickle Cell Disease | Recruiting | Procedure: haploidentical stem cell transplant Drug: Sirolimus, Campath, pentostatin, cyclophosphamide | National Heart, Lung, and Blood Institute (NHLBI) | 2 Years to 80 Years | Phase 1 Phase 2 | 88 | Interventional | 06-Apr-2017 | 30-Sep-2025 | United States |
| NCT00228631 | Analysis of T-Cell Immune Reconstitution Allogeneic Hematopoietic BMT | Completed | NA | Emory University | 6 Months to 21 Years | NA | 7 | Observational | Sep-2005 | Aug-2011 | United States |
| NCT03249831 | A Blood Stem Cell Transplant for Sickle Cell Disease | Recruiting | Drug: Cyclophosphamide Pentostatin, Rabbit anti-thymocyte globulin, TacrolimusMyco phenolatemofetil Biological: CD4+ T-cell-depleted HaploidenticalHematopoietic Transplant | City of Hope Medical Center | 18 Years to 45 Years | Phase 1 | 6 | Interventional | 04-Jan-2019 | Dec-2022 | United States |
| NCT02247843 | Stem Cell Gene Therapy for Sickle Cell Disease | Recruiting | βAS3-FB vector transduced peripheral blood CD34+ cells | Donald B. Kohn, M.D. University of California, Los Angeles | 18 years and older | Phase 1 Phase 2 | 6 | Interventional | Dec-2014 | Feb-2022 | United States |

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|--------------------|---|------------|---|---|----------------------|---------|-----|----------------|-------------|-------------|---------------|
| NCT00427661 | A Pilot Study of HSCT for Patients With High-risk Hemoglobinopathy Using a Nonmyeloablative Preparative Regimen | Completed | Busulfan; Fludarabine; cyclosporine and MMF | University of Pittsburgh | 3 Years to 35 Years | NA | 8 | Interventional | Jun-2002 | May-2014 | United States |
| NCT02989701 | Pilot and Feasibility Trial of Plerixafor for Hematopoietic Stem Cell (HSC) Mobilization in Patients With Sickle Cell Disease Pilot and Feasibility Trial of Plerixafor for Hematopoietic Stem Cell (HSC) Mobilization in Patients With Sickle Cell Disease | Completed | Plerixafor | Alessandra Biffi, Boston Children's Hospital | 18 Years to 35 Years | Phase 1 | 6 | Interventional | Jan-2017 | 11-Dec-2017 | United States |
| NCT02165007 | Haploidentical Hematopoietic Stem Cell Transplantation | Recruiting | peripheral blood stem cell graft that is CD34+ selected | Catherine Bollard, Children's National Research Institute | up to 22 Years | Phase 1 | 27 | Interventional | Jan-2015 | Nov-2022 | United States |
| NCT02105766 | Nonmyeloablative Peripheral Blood Mobilized Hematopoietic Precursor Cell Transplantation for Sickle Cell Disease and Beta-thalassemia in People With Higher Risk of Transplant | Recruiting | Drug: Alemtuzumab, Sirolimus, Cyclophosphamide, Pentostatin Procedure: Radiotherapy | National Heart, Lung, and Blood Institute (NHLBI) | 4 Years to 80 Years | Phase 2 | 162 | Interventional | 21-Apr-2014 | 31-Aug-2021 | United States |

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| | Failure | | | | | | | | | | | |
| NCT03664830 | Safety of Blood Stem Cell Mobilization With Plerixafor in Patients With Sickle Cell Disease (PISMO) | Recruiting | Plerixafor | City of Hope Medical Center | 18 Years to 40 Years | Phase 1 | 12 | Interventional | 19-Sep-2018 | Sep-2020 | United States | |
| NCT00004143 | Allogeneic Mixed Chimerism Stem Cell Transplant Using Campath for Hemoglobinopathies & Bone Marrow Failure Syndromes | Completed | Campath, Chemo, and/or TBI Allo SCT | David Rizzieri, MD, Duke University | 18 years and older | Phase 2 | 2 | Interventional | Sep-1999 | May-2008 | United States | |
| NCT03903289 | The Implementation of the Automated Erythrocytapheresis in Egyptian Sickle Cell Disease Center | Recruiting | Automated red cell exchange, Manual red cell exchange, Simple red cell transfusion | Ain Shams University | 2 Years to 30 Years | NA | 20 | Interventional | 16-Aug-2017 | 01-Jun-2020 | Egypt | |
| NCT00153985 | Allogeneic Stem Cell Transplantation Following Chemotherapy in Patients With Hemoglobinopathies | Completed | Procedure: Stem Cell Transfusion Drug: Busulfex, Fludarabine, Alemtuzumab | Dana-Farber Cancer Institute | 18 years and older | Phase 2 | 2 | Interventional | Mar-2004 | Mar-2008 | United States | |
| NCT04362293 | Reduced Intensity Transplantation for Severe Sickle Cell Disease | Recruiting | hydroxyurea, azathioprine, alemtuzumab, thiotepa, low dose total body irradiation, and | St. Jude Children's Research Hospital | 2 Years to 25 Years | Phase 2 | 40 | Interventional | 30-Apr-20 | 01-Jul-2024 | United States | |

| Sirolimus | | | | | | | | | | | | |
|--------------------|--|------------|--------------------------------------|---|---------------------------|-----------------|--------------|----------------|-------------|--------------|---------------|--|
| NCT00012545 | Collection and Storage of Umbilical Cord Stem Cells for Treatment of Sickle Cell Disease | Recruiting | NA | National Heart, Lung, and Blood Institute (NHLBI) | up to 45 Years | NA | NA | Observational | 01-Nov-01 | Not Provided | United States | |
| NCT00029393 | Induction of Stable Chimerism for Sickle Cell Anemia | Completed | HSCT | National Heart, Lung, and Blood Institute (NHLBI) | up to 100 Years | Phase 2 | Not Provided | Interventional | Aug-2001 | Jul-2007 | United States | |
| NCT03111589 | Monocytic Expression of Heme Oxidase-1 (HO-1) in Sickle Cell Patients and Correlation With the Humoral Immune Response to Vaccine and With Allo-immunization. | Completed | Inactivated influenza (H1N1) vaccine | Francis Corazza, Brugmann University Hospital | Child, Adult, Older Adult | NA | 102 | Interventional | Oct-2016 | Oct-2018 | Belgium | |
| NCT00730314 | Unrelated Hematopoietic Stem Cell Transplantation(HSCT) for Genetic Diseases of Blood Cells | Completed | HSCT | Children's Hospital Los Angeles | up to 21 Years | Phase 1 Phase 2 | 25 | Interventional | Aug-2008 | Aug-2015 | United States | |
| NCT03367546 | Haploidentical Allogeneic Hematopoietic Stem Cell Transplantation (HaploHCT) Following Reduced Intensity Conditioning (RIC) for Selected High-Risk Non-Malignant | Recruiting | BMT | Masonic Cancer Center, University of Minnesota | up to 25 Years | Phase 2 | 20 | Interventional | 02-Jul-2018 | Nov-25 | United States | |

Diseases

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|--------------------|--|------------|---------------------------------|--|----------------------|--------------------|----|----------------|-----------|-------------|---------------|
| NCT03709303 | Motivations, Expectations, and Decision-making of Sickle Cell Patients in Clinical Research | Completed | NA | National Institutes of Health Clinical Center (CC) | 18 years and older | NA | 27 | Observational | 29-Oct-18 | 31-Aug-2019 | United States |
| NCT02615847 | Clinical Trial to Study the Safety and Tolerability of MemantinMepha® in Sickle Cell Disease Patients (MemSID) | Completed | Memantinhydrochlorid | University of Zurich | 18 years and older | Phase 2 | 9 | Interventional | Aug-15 | 31-Mar-17 | Switzerland |
| NCT01950429 | Evaluation of Sickle Cell Liver Disease | Completed | NA | National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) | 18 Years to 99 Years | NA | 42 | Observational | 16-Oct-13 | 11-Jun-19 | United States |
| NCT00176852 | Stem Cell Transplant for Hemoglobinopathy | Completed | Busulfan, Fludarabine, ATG, TLI | Masonic Cancer Center, University of Minnesota | up to 50 Years | Phase 2 Phase 3 | 22 | Interventional | Jun-02 | Mar-14 | United States |
| NCT03513328 | Conditioning Regimen for Allogeneic Hematopoietic Stem-Cell Transplantation | Recruiting | Thiotepa | University of Florida | 3 Months to 39 Years | Phase 1 Phase 2 | 40 | Interventional | 15-Jun-18 | Jun-21 | United States |

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|--------------------|--|------------|---|---|---------------------|-----------------|-----|----------------|-----------|-----------|---------------|
| NCT03247218 | A Phase - IIa - IIb, Trial to Study the Safety, Tolerability, and Efficacy of Memantine as a Long-term Treatment of SCD (MeMAGEN) | Recruiting | Memantine Hydrochloride | HaEmek Medical Center, Israel | Ten years and older | Phase 2 | 40 | Interventional | 02-Feb-18 | 31-Dec-20 | Israel |
| NCT00957931 | Allo-HCT MUD for Non-malignant Red Blood Cell (RBC) Disorders: Sickle Cell, Thal, and DBA: Reduced Intensity Conditioning, Co-tx MSCs | Completed | BMT | Stanford University | 1 Year to 25 Years | Phase 2 | 6 | Interventional | Mar-09 | Aug-13 | United States |
| NCT00061568 | Improving the Results of Bone Marrow Transplantation for Patients With Severe Congenital Anemias | Recruiting | PBPC transplant | National Heart, Lung, and Blood Institute (NHLBI) | 2 Years to 65 Years | Phase 1 Phase 2 | 150 | Interventional | 16-Jul-04 | 31-Jan-21 | United States |
| NCT02179359 | Hematopoietic Stem Cell Transplant for High-Risk Hemoglobinopathies | Recruiting | Reduced Toxicity Ablative Regimen, Anti-thymocyte Globulin (ATG), Fludarabine, Busulfan | Masonic Cancer Center, University of Minnesota | up to 55 Years | NA | 25 | Interventional | 02-Sep-14 | Aug-21 | United States |
| NCT03333486 | Fludarabine Phosphate, Cyclophosphamide, Total Body Irradiation, and Donor Stem Cell Transplant in Treating Patients With Blood Cancer | Recruiting | Drug: Cyclophosphamide, Fludarabine Phosphate Procedure: Peripheral Blood Stem Cell Transplantation Radiation: Total-Body Irradiation | Roswell Park Cancer Institute | 1 Year to 75 Years | Phase 2 | 58 | Interventional | 07-Dec-17 | 06-Sep-23 | United States |

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|--------------------|---|------------|--|---|---------------------------|---------|-----|----------------|-----------|--------------|-----------------------|
| NCT00695123 | Screening for Subjects to Participate in Studies of Blood Disorders | Recruiting | NA | National Heart, Lung, and Blood Institute (NHLBI) | Child, Adult, Older Adult | NA | NA | Observational | 26-Jun-08 | Not Provided | United States |
| NCT03609840 | Study of Thiotepla and TEPA Drug Exposure in Pediatric Hematopoietic Stem Cell Transplant Patients | Recruiting | NA | University of California, San Francisco | up to 17 Years | NA | 60 | Observational | 10-Jan-18 | Jul-21 | United States |
| NCT02766465 | Bone Marrow Transplantation vs. Standard of Care in Patients With Severe Sickle Cell Disease (BMT CTN 1503) (STRIDE2) | Recruiting | Procedure: Hematopoietic Cell Transplant Drug: Busulfan, Fludarabine, r-ATG, Tacrolimus, Methotrexate, Alemtuzumab, Sirolimus, Melphalan, G-CSF | Medical College of Wisconsin | 15 Years to 40 Years | Phase 2 | 200 | Interventional | Nov-16 | Mar-22 | United States |
| NCT01917708 | Bone Marrow Transplant With Abatacept for Non-Malignant Diseases | Completed | Abatacept | Emory University | up to 21 Years | Phase 1 | 10 | Interventional | Jan-2014 | 19-Sep-19 | United States |
| NCT00029380 | Cord Blood Transplantation for Sickle Cell Anemia and Thalassemia | Completed | Procedure: Cord Blood Transplantation Drug: Sangstat, Cyclophosphamide, Busulfan, Mycophenolate Mofetil, Cyclosporine | National Heart, Lung, and Blood Institute (NHLBI) | 3 Years to 14 Years | Phase 2 | 30 | Interventional | Jan-1999 | Aug-2006 | Canada, United States |

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|--------------------|---|------------|--|--------------------------|----------------------|---------|----|----------------|-------------|----------|---------------|
| NCT01369160 | Curative Versus Disease-Modifying Therapies in Children With Severe Sickle Cell Disease (SCD_Cross) | Completed | NA | Emory University | 3 Years to 23 Years | NA | 33 | Observational | May-2005 | Mar-2014 | United States |
| NCT04293185 | A Study Evaluating Gene Therapy With BB305 Lentiviral Vector in Sickle Cell Disease | Recruiting | LentiGlobin BB305 Drug Product for SCD | bluebird bio | 2 Years to 50 Years | Phase 3 | 35 | Interventional | 14-Feb-2020 | Nov-2023 | United States |
| NCT02757885 | Transplantation Using Reduced Intensity Approach for Patients With Sickle Cell Disease From Mismatched Family Donors of Bone Marrow (TRANSFORM) | Recruiting | Procedure: Bone Marrow Transplant (BMT), Bone Marrow Harvest (Donation) Drug: Hydroxyurea, Thiotepa, Fludarabine monophosphate, Cyclophosphamide, Rabbit Anti-thymocyte Globulin Radiation: Total Body Irradiation | Emory University | 15 Years to 40 Years | Phase 2 | 15 | Interventional | Apr-2016 | Dec-2020 | United States |
| NCT01049854 | CD34+Selection for Partially Matched Family or Matched Unrelated Adult Donor Transplant | Completed | Thiotepa/Cyclophosphamide/ATG/Busulfan/Melphalan/Fludarabine/Alemtuzumab | New York Medical College | up to 70 Years | Phase 2 | 20 | Interventional | Sep-2011 | Aug-2018 | United States |

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|--------------------|---|-------------------------|--|---|----------------------|-----------------|-----|----------------|-------------|-------------|--|
| NCT03745287 | A Safety and Efficacy Study Evaluating CTX001 in Subjects With Severe Sickle Cell Disease | Recruiting | CTX001 | Vertex Pharmaceuticals Incorporated | 12 Years to 35 Years | Phase 1 Phase 2 | 45 | Interventional | 27-Nov-2018 | Feb-2021 | Belgium, Canada, Germany, Italy, United Kingdom, United States |
| NCT00919503 | Treosulfan and Fludarabine Phosphate Before Donor Stem Cell Transplant in Treating Patients With Nonmalignant Inherited Disorders | Recruiting | Procedure: Allogeneic Bone Marrow Transplantation Biological: Anti-Thymocyte Globulin Drug: Cyclosporine, Fludarabine Phosphate, Methotrexate, Mycophenolate Mofetil, Tacrolimus, Treosulfan | Fred Hutchinson Cancer Research Center | up to 49 Years | Phase 2 | 120 | Interventional | 31-Jul-2009 | 01-Feb-2023 | United States |
| NCT04628585 | Long-term Follow-up of Subjects With Sickle Cell Disease Treated With Ex Vivo Gene Therapy | Enrolling by invitation | NA | bluebird bio | 2 Years to 53 Years | NA | 85 | Observational | 21-Oct-2020 | May-2037 | France, United States |
| NCT03226691 | Peripheral Blood Stem Cell Collection for Sickle Cell Disease (SCD) Patients | Completed | Plerixafor | National Heart, Lung, and Blood Institute (NHLBI) | 18 years and older | Phase 1 | 15 | Interventional | 25-Jul-2017 | 27-Feb-2019 | United States |

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|--------------------|--|------------|---|----------------|----------------------|-----------------|----|----------------|-------------|-------------|---------------|
| NCT02061800 | CD34+ (Malignant) Stem Cell Selection for Patients Receiving Allogenic Stem Cell Transplant | Recruiting | Device: CliniMACS CD34+ Reagent System Drug: Thiotepa, Cyclophosphamide, Alemtuzumab, Tacrolimus, Melphalan, Busulfan, Fludarabine, Methylprednisolone | Diane George | up to 22 Years | Phase 1 Phase 2 | 15 | Interventional | 03-Jun-2013 | Dec-2021 | United States |
| NCT03282656 | Gene Transfer for Sickle Cell Disease | Recruiting | A single infusion of autologous bone marrow-derived CD34+ HSC cells transduced with the lentiviral vector containing a short-hairpin RNA targeting BCL11a | David Williams | 3 Years to 40 Years | Phase 1 | 15 | Interventional | 13-Feb-2018 | 13-Feb-2021 | United States |
| NCT04528355 | Data Collection Study of Patients With Non-Malignant Disorders Undergoing UCBT, BMT, or PBSCT With RIC (PRO-RIC) | Recruiting | NA | Paul Szabolcs | 2 Months to 60 Years | NA | 50 | Observational | 20-Aug-2020 | 30-Jun-2026 | United States |

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|--------------------|--|--|------------|--|---|---------------------------|---------|------|----------------|-------------|----------|---------------|
| NCT01962415 | Reduced Conditioning for Non-Malignant Undergoing BMT, or (HSCT+RIC) | Intensity for Non-Disorders UCBT, or PBSCT | Recruiting | UCBT: transfusion-dependent anemias or increased rejection risk, BMT, PBSCT, and not transfusion-dependent UCBT Drug: Hydroxyurea, Alectuzumab, Fludarabine, Melphalan, Thiotepa | Paul Szabolcs | 2 Months to 55 Years | Phase 1 | 100 | Interventional | 04-Feb-2014 | Nov-2022 | United States |
| NCT03904134 | Clinical Related Outcomes of Alternative Allogeneic Transplantation (BMT CTN 1702) | Transplant-Long-term of Donor | Recruiting | Donor Search Prognosis Score | Center for International Blood and Marrow Transplant Research | Child, Adult, Older Adult | NA | 1732 | Interventional | 14-Jun-2019 | Jun-2024 | United States |
| NCT03924401 | Acute Suppression Costimulation to Expand Non-malignant Transplant (ASCENT) | GVHD Using Blockade Non-Transplant | Recruiting | Abatacept | Emory University | up to 20 Years | Phase 2 | 28 | Interventional | 22-Aug-2019 | Dec-2023 | United States |

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|--------------------|---|-------------------------|-------------------------|---------------------------------------|----------------------|-----------------|----|----------------|-------------|-------------|---|
| NCT03964792 | Safety and Efficacy of Gene Therapy of the Sickle Cell Disease by Transplantation of an Autologous CD34+ Enriched Cell Fraction That Contains CD34+ Cells Transduced ex Vivo With the GLOBE1 Lentiviral Vector Expressing the β AS3 Globin Gene in Patients With Sickle Cell Disease (DREPAGLOBE) | Recruiting | DREPAGLOBE drug product | Assistance Publique Hôpitaux de Paris | 5 Years to 35 Years | Phase 1 Phase 2 | 10 | Interventional | 12-Nov-2019 | 12-Feb-2022 | France |
| NCT02633943 | Longterm Follow-up of Subjects With Hemoglobinopathies Treated With Ex Vivo Gene Therapy | Enrolling by invitation | NA | bluebird bio | up to 50 Years | NA | 94 | Observational | Sep-2013 | Mar-2031 | Australia , France, Germany , Italy, Thailand, United Kingdom , United States |
| NCT02186418 | Gene Transfer for Patients With Sickle Cell Disease | Recruiting | ARU-1801 | Aruvant Sciences GmbH | 18 Years to 45 Years | Phase 1 Phase 2 | 10 | Interventional | Jul-2014 | Jun-2023 | Canada, Jamaica, United States |

Table II: Summary of major Clinical trials of HSCT for SCD

| Study/Author | No.of patients target | median age | Duration | Regimen /Agent | Mechanism | Toxicity Grade | Overall survival (%) | Follow up time (In year) | EFS | Graft Rejection |
|--|--|------------|--------------------|--|------------------------------|----------------|----------------------|--------------------------|---------|-----------------|
| | | | | | | >III | 2 year | | >2years | |
| Krishnamurti et al., 2019 [44] | 17 5 | 22 | Jul 2012-Jun 2015 | HU, FLU, rabbit ATG, CsA , Tacrolimus, MTX | HLA- ID/AMD | 6 | 91% | 2.7 | 82% | 1 |
| Bolanos-Meade et al., 2019 [45] | 12 | 16 | Sept 2014-Aug 2017 | rabbit ATG, FLU, CY, | HLA-MSD | 6 | 86% | 1.9 | NA | 1 |
| Garcia morin et al., 2017 [46] | 11 | 7 | Jan 2010-Dec 2014 | HU, alemtuzumab, CY CsA, MTX | HLA- ID | 1 | 90.90% | 3.1 | NA | 1 |
| Shenoy et al 2016 [30] | 29 | 14 | Apr 2008-Apr 2014 | Alemtuzumab, FLU, Melphalan | HLA-AMD and URD | 13 | 79% | 2.2 | 69% | 3 |
| Bernaudin et al., 2019 [47] | 234 | 8.4 | Nov 1988-Dec 2012 | HU,CY, rabbit ATG (rabbit-ATG) | HLA-MSD-SCT | 12 | NA | 7.9 | 93.90% | 6 |
| Bhatia et al., 2014 [27] | 18 | 8.9 | NA | HU, FLU, Alemtuzumab | HLA-matched sibling allo-SCT | 7 | 100% | | 100% | 0 |
| Lucarelli et al., 2014 [25] | 13-non black African 27-black African | 13 10 | Jun 2004-May 2013 | HU,CY, rabbit-ATG | HLA-MSD-SCT | 2 5 | 91% NA | | 90% | 0 |

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|---|------------------------|------|--------------------|---|--------------------|--------------|-----------|------|------------|----|
| Dedeken et al., 2014 [17] | 50 | 8.3 | nov 1988-Mar 2013 | HU,CY, rabbit-ATG | HLA-ID | 5 | 94.10% | 7.7 | 85.6% (8y) | 4 |
| Hsieh et al., 2014 [48] | 30 | 28.5 | July 2004-Oct 2013 | MTX | HLA-ID | 0 | 97% | 3.4 | 87% | 4 |
| King et al., 2015 [49] | 43 | 13 | Mar 2003-May 2014 | FLU, Alemtuzumab, melphalan | | 12 | 93% | 3.42 | 91% | 2 |
| McPherson et al., 2011 [26] | 27 | 8.6 | Dec 1993-Aug 2007 | HU,CY, rabbit-ATG | HLA-MSD-SCT | 1 | 96% | 4.9 | 96% (5y) | 0 |
| Ruggeri et al., 2011 [31] | 16 | 6 | 1996-2009 | HU, melphalan, total-body irradiation (TBI) | HLA-ID | 3 | 94% | 3.08 | 50% | NA |
| Strocchio et al., 2015 [28] | 30 | 8.4 | Mar 2000-Mar 2014 | HU, <i>Treosulfan</i> , Thiotepa, FLU | HLA-ID | 0 | 100% (7y) | 10 | 93% (7y) | 2 |
| Dallas et al., 2013 [50] | 14-MRD graft | 11 | NA | HU,CY, horse ATG | HLA-MRD-HSCT | 4 | 93% | 9 | 93% | 0 |
| | 8-Haploidentical graft | 9 | | FLU, Thiotepa, HU, rabbit ATG, muromonab-CD3,CY | HLA-haploidentical | 0 | 75% | 7.4 | 38% | 8 |
| Matthes-Martin et al., 2013 [52] | 8 | 9 | 2004-2011 | ATG, Alemtuzumab, FLU, melphalan, thiotepa | HLA-ID | NON SPECIFIC | 90% | 4 | 95% | NA |
| Kamani et al., 2012 [32] | 8 | 13.7 | NA | Alemtuzumab, FLU, melphalan | | 0 | 87% | 1.8 | NA | 5 |

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|--------------------------------------|----|------|-------------------------|--|--------------------------|----|----------|------|------|----|
| Majumdar et al., 2010 [53] | 10 | 10.1 | Nov 1997- Jun 2005 | HU, horse ATG, CY, Alemtuzumab, FLU, melphalan | HLA-ID | 0 | 90% | 5.5 | 77% | NA |
| Panepinto et al., 2007 [29] | 67 | 10 | 1989-2002 | HU,CY | HLA-ID | 10 | 97% (5y) | 5.08 | 85% | 9 |
| Adamkiewicz et al., 2007 [54] | 7 | 2.4 | NA | BU, CY, ATG, FLU | HLA-ID | 2 | 86% | | 43% | 3 |
| Locatelli et al., 2003 [55] | 11 | 5 | Jun 1994-Jun 2001 | BU, CY, TT, ATG, FLU | HLA-ID | 0 | 100% | 2 | 90% | 1 |
| Walters et al., 2001 [56] | 59 | 10.1 | Sep 1991- April 2000 | BU, CY, ATG | HLA-ID | 11 | 93% | 3.5 | 84% | 5 |
| Ozdogu et al., 2018 [38] | 20 | 33 | Sep 2013-Oct 2017 | BU, CY, ATG, FLU | HLA-ID | 1 | 100% | 1.1 | NA | 0 |
| Brachet et al., 2004 [57] | 24 | 7.2 | 1988-2000 | BU, CY, ATG | HLA-ID- myeloablative | 3 | 93% | 8.7 | 96% | 2 |
| Maheshwari et al., 2013[51] | 16 | 6.2 | May 2014- May 2012 | Cytosan, ATG | HLA-ID | 0 | 100% | 3 | 100% | 0 |

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