Review Article *Iran J Ped Hematol Oncol. 2022, Vol 12, No 4, 272-302*

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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Received: 19 May 2021 **Accepted:** 13 May 2022

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).

[DOI: 10.18502/ijpho.v12i4.10918]

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

[DOI: 10.18502/ijpho.v12i4.10918]

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, whereassometrials 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

[DOI: 10.18502/ijpho.v12i4.10918]

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

[DOI: 10.18502/ijpho.v12i4.10918]

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.

[DOI: 10.18502/ijpho.v12i4.10918]

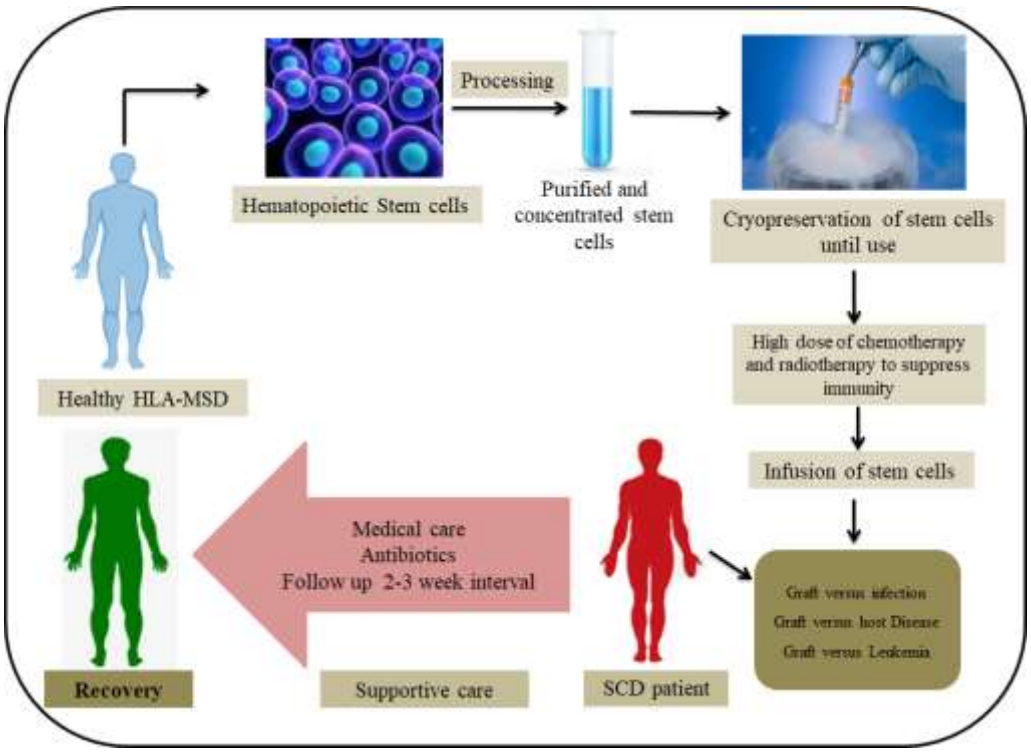

Figure 1. Overview of the HSCT procedure in sickle cell Anemia.

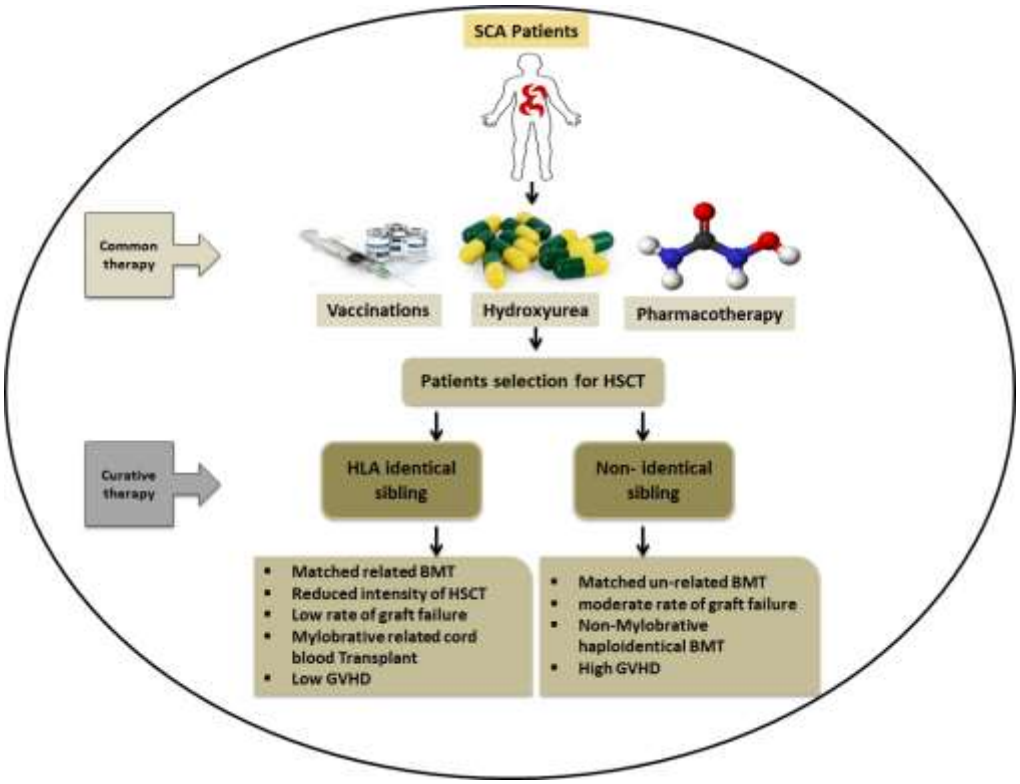

Figure 2. Flow of Approach inpatient's selection of HSCT for SCA

[DOI: 10.18502/ijpho.v12i4.10918]

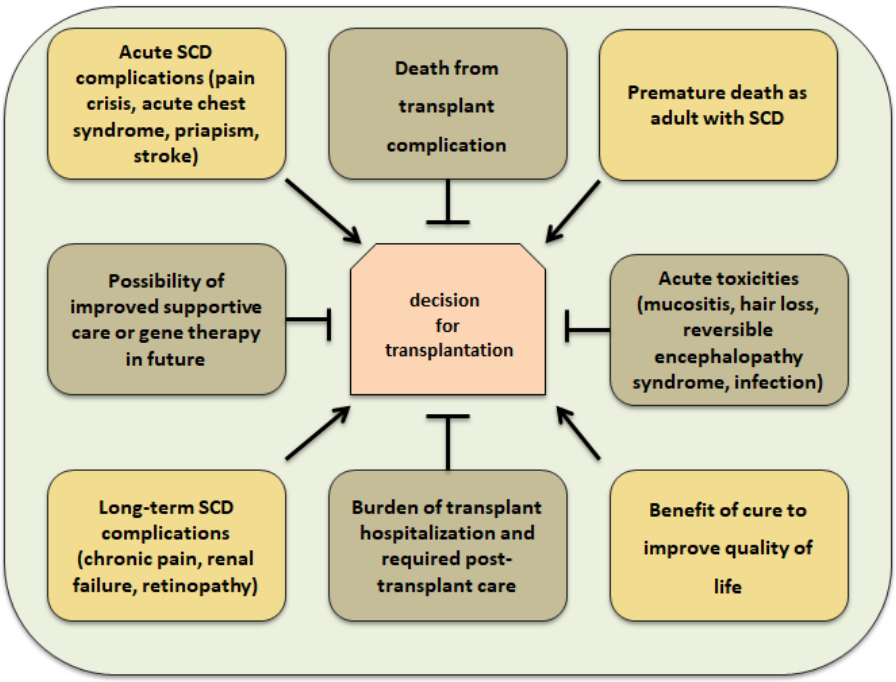

Figure 3: HSCT decision calculus. The final decision to undergo transplantation involves considering several potential risks, benefits, and other variables. A single SCA patient can evaluate each box differently. The figure is modified from (43)

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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	αβ+ T-cell depletion with MiltenyiCliniMACS 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,FludarabineMelphalan)	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	Bioverativ, a Sanofi company	18 Years to 40 Years	Phase 1 Phase 2	8	Interventional	28-Jun-f2019	Apr-2023	United States

[DOI: 10.18502/ijpho.v12i4.10918]

	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	Ph 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, Thiotepa	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, Mycophenolatemofetil, 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 Genoidentical 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

[DOI: 10.18502/ijpho.v12i4.10918]

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	NonmyeloablativeHaploidentical 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, TacrolimusMycophenolatemofetil 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 A 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

[DOI: 10.18502/ijpho.v12i4.10918]

	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

[DOI: 10.18502/ijpho.v12i4.10918]

			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 A (H1N1) virus 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

[DOI: 10.18502/ijpho.v12i4.10918]

	Diseases										
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

[DOI: 10.18502/ijpho.v12i4.10918]

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

[DOI: 10.18502/ijpho.v12i4.10918]

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 Thiotepa 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

[DOI: 10.18502/ijpho.v12i4.10918]

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

[DOI: 10.18502/ijpho.v12i4.10918]

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

[DOI: 10.18502/ijpho.v12i4.10918]

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 βAS3 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

[DOI: 10.18502/ijpho.v12i4.10918]

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	13	Jun 2004-May 2013	HU,CY, rabbit-ATG	HLA-MSD-SCT	2	91%		90%	0
	27-black African	10				5	NA			

[DOI: 10.18502/ijpho.v12i4.10918]

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
Ruggreri 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, *Treosulfan* ,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

[DOI: 10.18502/ijpho.v12i4.10918]

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	Cytoxan, ATG	HLA-ID	0	100%	3	100%	0

[DOI: 10.18502/ijpho.v12i4.10918]

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[DOI: 10.18502/ijpho.v12i4.10918]