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Allogeneic Transplant and Gene Therapy: Evolving Toward a Cure.

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Journal

Hematology / Oncology Clinics of North America, 36(6)

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Publication Date

2022-12-01

DOI

10.1016/j.hoc.2022.06.007

Peer reviewed



HHS Public Access

Author manuscript

Hematol Oncol Clin North Am. Author manuscript; available in PMC 2023 December 01.

Published in final edited form as:

Hematol Oncol Clin North Am. 2022 December ; 36(6): 1313–1335. doi:10.1016/j.hoc.2022.06.007.

Allogeneic transplant and Gene therapy: evolving towards a cure

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Keywords

Allogeneic transplant; Hematopoietic cell transplant; Haploidentical; Matched sibling donor; Gene therapy; Gene editing; Sickle cell disease; Graft versus host disease

Introduction:

In sickle cell disease (SCD), an abnormal beta-globin gene with a missense mutation leads to hemoglobin polymerization and sickling within the red blood cell (RBC)¹, associated with extensive morbidity and early mortality^{2–4}. With the advent of newborn screening, penicillin prophylaxis, and pneumococcal vaccination, the mortality rate in children has decreased. However, the median survival for adults in SCD has not improved^{4, 5}. Risk factors for early mortality in adults include elevated tricuspid regurgitant jet velocity (TRV), renal failure, and lung impairment^{6, 7}. Current SCD-directed drug therapies include hydroxyurea (HU), l-glutamine, voxelotor, and crizanlizumab. However, none of these pharmaceutical agents offer a cure⁸.

Successful hematopoietic cell transplant (HCT) interrupts the progression of SCD-related complications, changes the patient's genotype from SCD to donor HbAA or HbAS, establishes donor-derived erythropoiesis, and can stabilize or restore organ function^{9, 10}. Hence, HCT is an important curative option for individuals with SCD. SCD HCT can be allogeneic or autologous. In allogeneic HCT, the source of donor hematopoietic cells is from

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Disclosure Statement- MCW has consulting agreements with All Cells, Inc, BioChip Labs, Inc, Ensoma, Inc and Vertex Pharmaceuticals.

a human leukocyte antigen- (HLA) matched sibling donor (MSD), HLA-haploidentical, umbilical cord blood (UCB), or HLA-matched unrelated donor (MUD).

There is a range of conditioning regimen intensity, such as myeloablative, reduced-intensity conditioning (RIC), and non-myeloablative (NMA) regimens. Myeloablative conditioning includes high-dose chemotherapy, which is generally limited to children or adults without significant organ damage. Infertility is a major concern after myeloablative conditioning. RIC uses lower doses of chemotherapy which may preserve gonadal function. However, myeloablative or RIC can lead to graft-versus-host disease (GVHD)¹¹. Non-myeloablative HCT employs intensive immunosuppression to decrease the risk of graft rejection and GVHD while preserving fertility. While the risk of GVHD may be lower, the graft rejection rate can be higher¹² after NMA conditioning.

Patients who undergo gene-modified autologous HCT receive their own hematopoietic stem and progenitor cells (HSPCs). These genetically engineered autologous cells eliminate the need for immunosuppression and, more importantly, the risks of GVHD and immune-mediated graft rejection^{13, 14}. Nevertheless, the need for myeloablative chemotherapy currently limits this treatment to those with suitable organ function.

Four curative options are used most commonly in individuals with SCD: MSD HCT, HLA-haploidentical HCT, and autologous gene therapy and gene editing. Here we review the risks and benefits of these four curative options and summarize progress that has been made in the past five years.

HLA MSD HCT

Pediatric

Indications for MSD HCT in children with SCD have traditionally included stroke, elevated transcranial doppler (>200 m/s), or recurrent VOC despite HU^{15, 16}. In 1996, a pediatric multi-center myeloablative HLA MSD HCT trial for SCD showed overall survival (OS) and EFS of 91% and 73%, respectively at four-years of follow-up¹⁰. Bernaudin et al. in 2007 reported 93.1% OS and 86.1% EFS with at least two years of follow-up. Twenty percent of the patients had grade II or higher acute GVHD (aGVHD), and 12.6% had chronic GVHD (cGVHD). The authors noted that adding anti-thymocyte globulin (ATG) to busulfan and cyclophosphamide decreased the graft rejection rate from 22.6% to 2.9%¹⁷.

More recently, a compilation of single-center patient series including more than 800 patients (age range 1.7–20.3 years) reported an OS of 95% and EFS of 92% for pediatric myeloablative MSD HCT¹⁶. Still, 7–40% developed aGVHD, and 5–20% developed cGVHD. Registry data gathered by the Center for International Blood and Marrow Transplant Research showed the risk for aGVHD and cGVHD was higher with increasing age; a similar trend was seen with age and EFS, OS, graft failure, and death¹⁸. Further, decreased EFS and higher mortality, aGVHD, and chronic GVHD were shown in patients 13 years with RIC compared to NMA regimens¹⁹. There was no significant difference in outcome after myeloablative and NMA conditioning. Brazauskas et al. stratified SCD HCT patients according to good, intermediate, and high-risk groups based on their EFS.

Patients <12 years old with MSD were in the good-risk group, followed by patients <12 with unrelated donors, then patients >13 years with MSD, and lastly, patients >13 years with unrelated donors²⁰. The 3-year EFS was >90% in the good-risk group compared with ~60% in the high-risk group, which included patients >12 years who received mismatched donor HCT. Graft failure was significantly higher in the high-risk group (21–38%), compared with 6% graft failure in the good-risk group.

At least 12 MSD HCT studies in the last five years show improved EFS and OS in the pediatric population (Table 1). These studies include patients with an age range of 0.3–28.9 years. The conditioning regimens vary among studies, and the median follow-up was 41 months across all the studies. OS and EFS range from 71.4–100% and 67–100%. The overall incidence of aGVHD ranged from 0–57%. While the study by Ngwube et al. showed 57% cGVHD, all but one patient had mild/limited cGVHD¹⁸. Although, the above historical studies have similar outcomes as the newer studies listed in Table 1, more recent studies report improved EFS and OS as noted in the three large registry studies (with EFS ranging from 90.7% to 93.9% and OS ranging from 95% to 97%)^{18, 19, 43}.

Adult

Early clinical trials of MSD HCT in adults involved myeloablative conditioning. The first attempt to cure adults with MSD HCT involved myeloablative conditioning in two patients who were 40 and 56 years of age²¹. After prompt donor engraftment, they died of GVHD. Myeloablative chemotherapy also excludes HCT in SCD adults with impaired renal function, decreased pulmonary function, cirrhosis, pulmonary hypertension, and poor Karnofsky Performance Status (KPS <70). Therefore, the National Institutes of Health (NIH), focused on NMA MSD HCT in lieu of myeloablative chemotherapy in adults with irreversible end-organ damage such as stroke, elevated TRV (>2.5 m/s), pulmonary hypertension, chronic renal insufficiency, sickle hepatopathy, and reversible complications not ameliorated by HU. The approach utilized a minimal toxicity regimen of alemtuzumab, 300 cGy total body irradiation (TBI), and sirolimus to elicit an immunoablative effect in lieu of myeloablation to mitigate risks of GVHD and graft failure and to lower the risk of transplant-related morbidity and mortality. The first report in 2009 showed an OS of 100% and an EFS of 90%²² with 30 months follow up. Notably, no one developed GVHD. An expanded update with this regimen included three sites with 122 patients. With a median follow-up of 4 years, the OS was 93%, and EFS was 85%, with no grade III to IV aGVHD and no cGVHD⁸. Therefore, HCT of adults with SCD is feasible and practical with this regimen.

In the past five years, results from 4 studies of MSD HCT in adults (up to age 65 years) have been reported. The overall median follow-up was 40.2 months (Table 1). One hundred fifty-nine patients received varying conditioning regimens. OS ranged from 93–100%, with 87–100% EFS. The incidence of aGVHD and cGVHD was 2–18% and 0–29%, respectively. Therefore, NMA HLA-matched sibling HCT can be performed safely in adults with comorbidities²³. Unfortunately, the constraint of lacking a MSD and an adverse risk profile in older adults have limited access to this curative option in most patients. This underscores the need for new studies to expand donor availability and improve patient outcomes.

Haploidentical HCT

Pediatric

Most patients will have an HLA-haploidentical donor²⁴. In 2013, the first pediatric HLA-haploidentical HCT study for SCD was reported²⁵. Eight patients < 14 years of age received myeloablative conditioning, and all patients had a history of stroke. At seven years of follow-up, OS was 75%, and EFS was 38%. Four patients experienced aGVHD, and 3 had cGVHD²⁵.

In the last five years, approximately 100 pediatric patients have received HLA-haploidentical HCT with an overall median follow-up of 21.5 months (Table 2). The conditioning regimens varied across these patient series; most included ATG, fludarabine, and thiotepa and 4 utilized post-transplant cyclophosphamide (PT-Cy) to abrogate host-versus-graft and graft-versus-host reactions. Overall survival and EFS have improved to 84–100%. However, the incidence of aGVHD after haploidentical HCT is about twice the rate of aGVHD observed after MSD HCT in children (Table 2). The cumulative incidence of haploidentical HCT cGVHD is similar to MSD HCT in the pediatric population. Although the study by Pawlowska et al.²⁶ had a high cGVHD rate at 75%, this series included 3 patients who had mild, limited skin GVHD that responded to therapy. The total sample size of the haploidentical HCT retrospective cohort is smaller than the MSD HCT experience. Hence, there is a need for additional studies to assess outcomes after HLA-haploidentical HCT in children. There is an ongoing multicenter clinical trial conducted through the Blood and Marrow Transplant Clinical Trials Network that is evaluating a reduced intensity regimen with PT-Cy in children with severe SCD.

Adult

The Hopkins group reported the first haploidentical study for adults with SCD in 2012¹². Indications for HCT included stroke, ACS requiring exchange transfusion or hospitalization, recurrent VOC, stage I or II sickle lung disease, red cell alloimmunization, history of invasive pneumococcal disease, or transfusion-dependence. Fourteen patients, including 2 patients less than 18 years, received conditioning with pre-HCT cyclophosphamide, fludarabine, ATG, TBI 200cGy, and PT-Cy. Importantly, all patients survived, and none developed acute or chronic GVHD 2 years post-HCT. However, 6 patients (43%) experienced acute graft rejection, and a seventh patient with low donor chimerism levels had persistent transfusion-dependent anemia after HCT¹².

In parallel, the NIH group enrolled SCD patients with severe comorbidities, including end-stage renal disease requiring dialysis, pulmonary hypertension, heart failure, and cirrhosis²³. The NMA conditioning regimen utilized in the MSD HCT setting, based on murine data, was modified to accommodate these patients with severe disease²⁷. The study included three cohorts with increasing doses of PT-Cy. Twenty-three patients who were 20 to 56 years of age were enrolled. Twenty-one had SCD, and two had transfusion-dependent beta-thalassemia. None of the patients died before 100 days post-HCT, and OS was 86%²³. The addition of PT-Cy improved the engraftment rate from 33% with no PT-Cy to 83% with 100mg/kg PT-Cy. The EFS increased from 0% after no PT-Cy to 50% with 100mg/kg

PT-Cy. While none of the patients experienced moderate to severe GVHD, the graft rejection rate was unacceptably high²⁸.

A compilation of recent studies of HLA- haploidentical HCT in adults with severe SCD over the past five years showed OS at 87–100% and EFS of 50–93%, with an overall median follow-up of 20.6 months (Table 2). The study with the lowest OS and EFS was the initial study referenced above in 2017. While the aGVHD rate ranged from 8.3–33%, most aGVHD was grade II. The cGVHD rate spanned 8.3–16%. An extended period of follow-up will be necessary to assess the efficacy of HLA- haploidentical HCT in adults, but this curative option has the potential to expand the donor pool for SCD patients who might benefit from HCT.

Future of Allogeneic HCT in SCD

Table 3 shows active and planned clinical trials of MSD HCT and haploidentical HCT for SCD. The MSD trials in children focus on decreasing toxicity by administering less intensive conditioning, a strategy that will be monitored carefully for the incidence of graft failure. In adults, efforts aim to improve long-term EFS by reducing GVHD through minimal toxicity regimens (low-dose total body irradiation and alemtuzumab). Three pediatric HLA-haploidentical HCT trials focus on T cell depletion and reduced-intensity conditioning.

Similarly, trials of HLA-haploidentical HCT in adults are focused on decreasing toxicity and reducing GVHD by applying pre-transplant immunosuppression in lieu of myeloablation, and ex vivo depletion of T cells with CD34+ selection²⁹. Another study compared RIC MSD HCT with standard non-curative disease-modifying therapies. While still in the early phase of clinical development, an antibody-based myeloablative study selectively targeting hematopoietic stem cells using CD117 antibody-drug-conjugates is being pursued and is particularly applicable in non-malignant disorders such as SCD³⁰. If successful, non-chemotherapy conditioning could expand the number of patients eligible for allogeneic HCT and autologous gene-based therapy for SCD.

Unrelated donors (URD) also contribute to expanding the donor pool, where SCD patients have a 57% chance of finding minimally HLA mismatched donors in registries (defined as HLA-matched at 7 of 8 or 8 of 8 HLA alleles)³¹. However, the risk of aGVHD, cGVHD, and transplant-related mortality in the first URD SCT trial with a 2-year OS of 79% dampened enthusiasm for this particular reduced-intensity regimen³². Efforts to reduce GVHD risks have focused on PT-Cy³³ and the use of abatacept. Inhibition of T-cell co-stimulation with abatacept was studied in 14 patients with a median follow-up of 1.6 years³⁴. Seven of the 14 patients had a URD. Abatacept supplemented tacrolimus and methotrexate for GVHD prophylaxis. The median age at HCT was 13 years (range, 7–21 years), and the 2-year probability of OS and EFS was 100% and 92.9%, respectively. At day +100, the incidence of grade II to IV and grades III to IV aGVHD was 28.6% and 7%, respectively. The one-year incidence of cGVHD was 57%, which was mild/limited in all but one patient. Another study reported both OS and EFS were 100% at two years post MSD and MUD HCT⁵¹. The median age at HCT was 11 (3–21) years; one patient developed

grade III-IV aGVHD and cGVHD in 5 patients. Altogether, these studies are promising for a role in decreasing GVHD after MUD HCT for SCD.

Autologous Gene Addition and Editing Therapies for SCD

Like HLA-haploidentical HCT, autologous gene therapy also expands the donor pool since patients serve as their own donors. However, much less is known about the long-term toxicities and durability of gene therapy compared with allogeneic HCT for SCD. Replacement gene therapy and gene editing rely upon the mobilization and collection of CD34+ HSPCs, isolation of the CD34+ cells followed by random genomic insertion of a gene addition lentiviral vector or modification of a targeted genomic sequence by gene editing reagents introduced by electroporation. The most common strategy utilizes the expression of an anti-sickling globin that generates fetal hemoglobin-like properties. A second strategy targets inactivation of an intronic erythroid-specific enhancer in BCL11a to induce high-level fetal globin expression due to BCL11a repression. BCL11a is a major fetal hemoglobin (HbF) repressor at birth (reviewed in¹⁴). Published reports suggest that both strategies have successfully reduced episodes of severe vaso-occlusive pain and markers of hemolysis in SCD^{35–37}. In these clinical trials, the typical toxicity profile mimics that predicted by the administration of myeloablative busulfan that precedes the infusion of the genome-modified HSPCs. There have been no reports of failure of the modified cells to engraft. Bone marrow harvesting has been replaced by using single-agent plerixafor-mobilized HSPCs, which has improved the therapeutic effect of the drug product^{13, 38}. Use of granulocyte-colony stimulating factor (G-CSF), although standard in other settings, is contraindicated in SCD outside of allogeneic HCT due to the risk of triggering VOC, multi-organ failure, and death³⁹.

The gene therapy results in SCD, using the BB305 lentiviral vector, were reported recently³⁷. Thirty-five patients with severe SCD received autologous CD34+ HSPCs after transduction with a lentiviral vector that expresses the anti-sickling hemoglobin, HbAT87Q. Post-infusion levels of the anti-sickling hemoglobin reached a plateau by 1–3 months post-infusion and were stable through 3 years of median follow-up. These levels generated a median total hemoglobin value that increased from 8.5 gm/dL at baseline to 11.0 gm/dL or more at six months, and HbAT87Q contributed to 40% or more of the total hemoglobin. Of interest, the HbAT87Q had a nearly pan-cellular RBC distribution. There was a mean of 85±8% of RBC with at least some HbAT87Q at 24 months balanced by roughly 15% of RBC that contained only HbS, the latter of which would be at risk for sickling. In the HbAT87Q-containing RBC population, the median HbAT87Q ranged from 11.7 to 22.7 pg per RBC, approximating the range of 13 to 18 pg per RBC of HbA present in the sickle trait RBC. This anti-sickling hemoglobin distribution would predict a clinical phenotype of sickle cell trait, which was supported by the clinical outcomes. Markers of hemolysis such as serum bilirubin, haptoglobin, lactate dehydrogenase (LDH), and reticulocyte count all approached normal levels or were improved compared with baseline, post-infusion. In patients who had at least six months of follow-up post-infusion, there was a cessation of severe vaso-occlusive painful events, defined as a hospitalization or administration of intravenous analgesics in an ambulatory setting. There was a median of 3.5 events per year (range, 2.0 to 13.5) 2 years before enrollment that declined to a median of 0 per year

(range, 0 to 5.9) (Figure 1). Notably, there were no strokes reported in the follow-up period, including patients at risk of stroke. These preliminary results showed near correction of the SCD phenotype after a one-time infusion of the lentiviral transduced autologous HSPCs.

Parallel studies in gene therapy/gene editing aimed at inducing HbF have shown a similar toxicity profile after myeloablative busulfan and infusion of the modified HSPCs. One approach for HbF induction utilizes a lentiviral vector to express an inhibitory sequence embedded in a short hairpin microRNA (shmiR) that targets BCL11a mRNA for post-transcriptional silencing³⁵. Because expression of the shmiR is under the control of erythroid-specific regulatory elements, BCL11a inhibition only occurs in the erythroid lineage. Six patients treated with the vector have had high-level, sustained HbF expression post-infusion. The serum hemoglobin increased from 9.3 to 11.4 gm/dL in the five patients not treated by RBC transfusions with a HbF percentage of 30.4% (range, 21.6 to 40.0). Markers of hemolysis also declined from baseline but were not normalized. None of the 6 patients had a severe vaso-occlusive episode, ACS, or stroke post-infusion.

A second approach for inducing HbF utilizes engineered CRISPR gene editing reagents to inactivate the same intronic erythroid-specific enhancer in BCL11a³⁶. In a case report, a patient with SCD had robust HbF induction and stable expression in the peripheral blood, eliminating vaso-occlusive events and the need for RBC transfusions. Together, both strategies for HbF induction by BCL11a inactivation in erythroid cells appear feasible and effective.

Finally, another approach using CRISPR technology to correct the sickle mutation directly by homology-directed repair has generated compelling pre-clinical evidence of safety and efficacy. This approach will also be investigated in early phase clinical trials^{40, 41}.

Risk of Acute Myelogenous Leukemia after Curative Therapy

Myeloid malignancies post NMA allogeneic HCT for SCD were reported in 3 of 76 patients at the NIH⁴². These arose in the setting of graft failure and, in two out of the three adult patients, pathogenic *TP53* mutations detected at baseline prior to HCT increased in size over time until the development of overt malignancy. Pediatric patients have thus far fared better with little to no reports of hematologic malignancies. For example, in a study of 234 patients, with a median age 8.4 years and a median follow-up of about eight years after myeloablative MSD HCT, including 44% with mixed chimerism, no one developed a myeloid malignancy⁴³.

Enthusiasm for autologous gene therapy has been tempered by the observation of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in 2 of 47 participants with SCD treated in the lentiviral gene therapy trial with Lentiglobin®^{44, 45}. In both cases, the source of CD34+ cells was bone marrow. In subsequent patients, plerixafor-mobilized peripheral blood has replaced marrow as the source of CD34+ cells, due in part to increased CD34+ cell yield. Both patients developed monosomy 7 and acquired driver mutations in *RUNX1* and *PTPN11*, and an additional *KRAS* mutation in one case, 3 – 5 years post-infusion. Both patients died of AML. The driver mutations were not detected in the pretreatment samples. In the first case, no vector was seen in the leukemic

blast population; thus residual host cells exposed to the alkylating agent busulfan might have conferred treatment-related AML. In the second case, however, vector was present in leukemic blasts with integration near the *VAMP4* gene, which is not associated with acute leukemia. The vector did not increase gene expression of *VAMP4*, and gene expression across the 10-megabase region flanking *VAMP4* was not altered by vector insertion. It was determined that vector insertion was not the cause of AML⁴⁵, but shown that the leukemic clone was in the transfected pool and thus not exposed to high dose busulfan.

The possibility of an association of AML with SCD has been suggested by retrospective registry data that show an increased risk of AML in SCD, although AML is still rare in this population^{46, 47}. There is speculation that this association might be promoted by the inflammatory milieu and oxidative stress of hematopoiesis in the marrow niche that is characteristic of SCD. The selection of clonal hematopoiesis with driver mutations that exert a proliferative advantage in this milieu might also emerge after competitive repopulation of gene-modified HSCs following myeloablation and autologous HCT⁴⁸. The basis for these observations is under investigation. It will be imperative to better inform patients about the long-term risk of clonal hematopoiesis and AML after gene therapy and, more broadly, after any curative therapy⁴². There are efforts to incorporate genomic screening to assess risk before gene therapy.

Conclusions

Several new curative therapies have arisen for SCD beyond MSD HCT, including haploidentical HCT, gene therapy, and gene editing. However, compelling comparative information is not yet available for individuals lacking a MSD that would facilitate selecting one curative therapy over another. The success rate of HCT in the pediatric population with HLA-matched donors is promising^{18, 23, 33, 49, 50}. However, GVHD continues to be an obstacle. Continued efforts will be needed to decrease the graft failure rate after MSD HCT for adults and to decrease graft rejection and GVHD in adults and children undergoing HLA-haploidentical HCT. While autologous gene therapy and gene editing avoid immune complications such as GVHD and graft rejection, they rely upon myeloablative chemotherapy, which excludes most older adults who have begun to experience cumulative organ toxicity from SCD from this potentially curative option. Further, enthusiasm for gene therapy and certain allogeneic approaches are tempered by the risk of treatment-related myeloid malignancies. Screening tools might be developed to predict myeloid malignancy development in the future, but screening criteria do not currently exist. There is also considerable uncertainty about how to accomplish access to curative therapies outside of resource-rich countries. Thus, additional research must be conducted, and health policies must be enacted to ensure patient safety and equitable access to these novel curative therapies. Lastly, curative therapy studies are greatly limited by lack of long-term efficacy and safety data. These data will be critical to developing a personalized approach to curative therapy for individuals with SCD.

Acknowledgements:

This work was supported by the Intramural Research Program of the National Heart, Lung, and Blood Institute (NHLBI) and the Cooperative Study of Late Effects for SCD Curative Therapies (COALESCE, 1U01HL156620-01, NHLBI), National Institutes of Health.

Glossary

SCD	sickle cell disease
RBC	red blood cell
MSD	matched sibling donor
HCT	hematopoietic cell transplant
HLA	human leukocyte antigen
GVHD	graft-versus-host disease
aGVHD	acute graft-versus-host disease
cGVHD	chronic graft-versus-host disease
RBC	red blood cell
TRV	tricuspid regurgitant jet velocity
HU	hydroxyurea
URD	unrelated donors
HSPCs	hematopoietic stem and progenitor cells
AML	acute myeloid leukemia
VOC	vaso-occlusive crises
PTIS	pre-transplant immunosuppression
PT-Cy	post-transplant cyclophosphamide
OS	overall survival
EFS	event-free survival
ATG	anti-thymocyte globulin
RIC	reduced intensity conditioning
KPS	Karnofsky Performance Status
NIH	National Institutes of Health
NMA	non- myeloablative
HbF	fetal hemoglobin

MUD	matched unrelated donor
UCB	umbilical cord blood
TBI	total body irradiation
GCSF	granulocyte-colony stimulating factor
LDH	lactate dehydrogenase
shmiR	short hairpin microRNA
MDS	myelodysplastic syndrome

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Key Points

- Review the efficacy of curative therapy for SCD
- Study the toxicity associated with curative therapy for SCD
- Evaluate the two most utilized allogeneic HCT options, MSD and haploidentical, and gene therapy and gene editing for SCD
- Highlight progress made in curative therapy studies over the last 5 years for SCD

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Synopsis

Curative therapies for sickle cell disease (SCD) now encompass human leukocyte antigen (HLA)-haploidentical hematopoietic cell transplant (HCT) and gene therapy, which have the potential to expand access. However, comparative trial data that might facilitate selecting one curative therapy over another are unavailable. While HLA-matched sibling donor (MSD) HCT in children is successful in 90 – 95% of patients, it is rarely available. New strategies to decrease graft rejection and graft-versus-host disease (GVHD) risks are needed to expand HLA-haploidentical HCT. Autologous gene therapy with myeloablation also has limitations, but eliminates problems of GVHD and graft rejection. Herein, we review recent studies on curative therapies in the past 5 years.

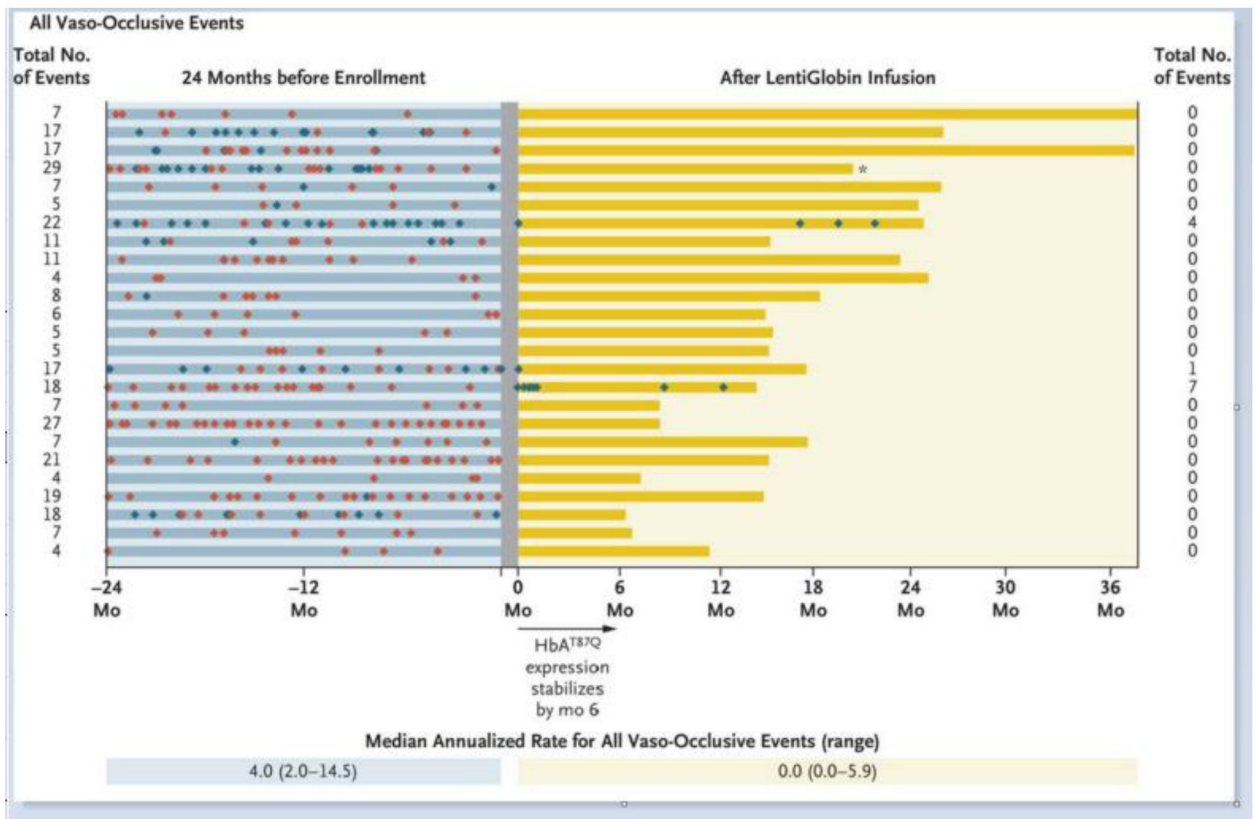


FIGURE 1:

Changes in the Rate of Vaso-Occlusive Events before and after LentiGlobin Infusion. All vaso-occlusive events after the LentiGlobin infusion are presented. The gray shade indicates the period before infusion when transfusions were administered. Red and blue diamonds represent severe and non-severe vaso-occlusive pain events, respectively. From Kanter J, Walters MC, Krishnamurti L, et al. Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease. *N Engl J Med.* 2022;386(7):617–628.

Table 1A

Summary of recent publications on HLA matched sibling donor hematopoietic cell transplant for sickle cell disease (2017–2022)

Reference	Size	Median Age (range) years	Graft Source	Conditioning Regimen	Median follow up, months (range)	GVHD	Graft Failure	EFS	OS
*Gluckman et al 2017	846	8.3 (0.3–16.0)	BM/PBS C/UCB	varied	56.4 (0.3–324.6)	NA acute, 13.3% chronic	NA	93%	95%
Marzollo et al 2017	7	6.5(4–16.3)	BM	Tre/Thio/Flu/ATG	28.2(9.6–78)	0% acute, 0% chronic	0%	100%	100%
Garcia et al., 2017	11	7 (2–13)	BM	BU/Alem/CY	37.2 (12–68.4)	54% acute, 0% chronic	0%	82%	91%
Park et al 2018	7	12.5 (6.9–16.9)	PBSC	Bu/Cy/ATG	34 (22–47)	57% acute, 47.6% chronic	0%	NA	71.4%
Alonso et al., 2019	22	8.6(2.09–15)	BM	Bu/Cy	36 (NR)	31.8% acute, 13.6% chronic	0%	79%	85%
Guilcher et al 2019	16	12 (3 – 18)	PBSC	Alem/TBI 300cGY	19.5 (15.2–27.8)	0% acute, 0% chronic	12.5%	100%	100%
*Eapen et al 2019	558	11 (6–17)	BM/PBS C/UCB	varied	36 (18–60)	6.2% acute, 18.1% chronic	6%	90.7%	96.2%
*Bernaudin et al 2020	234	8.4 (2.2–28.9)	BM/PBS C/UCB	Bu/Cy/ATG	94.8(1.2–331.2)	20% acute, 10% chronic	0.90%	93.9%	97%
Ngwube et al 2020	14	13 (7–21)	BM	Alem/Flu/Mel ± Thio	19.2 (12–65.9)	28.6% acute, 57% chronic	0.07%	92.9%	100%
Sahdev et al 2020	9	10 (5–19)	BM	Late Alem//Flu/Mel	108 (102–120)	43% acute, 25% chronic	33%	67%	100%
Sahdev et al 2020	16	6.5 (4–17)	BM	Early Alem/Flu/Mel	54 (21.6–102)	11% acute, 0% chronic	0%	94%	94%
Oostenbrink et. al 2021	12	9.7 (1.3–18.0)	BM	Flu/Thio/Treo/ATG	30 (0.4–36)	NA acute, 16.7% chronic	13%	79%	96%
John et. al 2021	38	8.6 (1.7–19.9).	BM	Bu/Cy/Alem	57.6 (2.4–204)	7.8% acute, 15.8% chronic	0%	94.7%	94.7%
Carabant et al 2021	45	9.13 (2.01–19.08)	BM	Bu/Cy or Treo/Flu/Thio	41 (10–246)	6.8% acute, 5.4% chronic	4%	89.4%	92.1%
Kogel et.al 2021	17	10.71 (1–20)	BM	Bu/CyorFlu/Thio/Treo, or Flu/Thio/Mel	90.25 (18.75–208)	NA acute, 0% chronic	1%	94%	100%

* Registry studies, data include cases reported in the individual series.

Abbreviations: BM: bone marrow, PBSC: peripheral blood stem cell, UCB: umbilical cord blood, Treo, treosulfan, Thio thiotepa, Flu: fludarabine, ATG: anti-thymocyte globulin, BU: busulfan, Alem: alemtuzumab, Cy: cyclophosphamide, TBI: total body irradiation, cGY: centigray, Mel: melphalan, NR: not reported, NA: not available

Table 1B

Summary of recent publications on HLA matched sibling donor hematopoietic cell transplant for sickle cell disease (2017–2022)

Reference	Adult Size	Median Age years (range)	Graft Source	Conditioning Regimen	Median Follow up, months (range)	GVHD	Graft Failure	EFS	OS
*Gluckman et al 2017	154	19.3 (16.0– 54.4)	BM/ PBSC	varied	48.0 (2.18– 305.9)	NA acute, 19.6% chronic	NA	81%	81%
Ozdogu et al 2018	20	33.4 (20– 45)	PBSC	Flu/Bu/ATG/TBI 200 cGy/PT-Cy	13.8 (0.3– 50)	5% acute, 0% chronic	0%	100%	100%
Krishnamurti et al 2019	17	(17–36)	PBSC	Flu/Bu/ATG	32.4 (26.4– 60)	18% acute, 29% chronic	0%	94%	94%
Alzahrani et al 2021	122	(10–65)	PBSC	TBI 300 cGy, Alem	(7.2–180)	2% acute, 0% chronic	13%	87%	93%

* Registry studies, data includes cases reported in the individual series.

Abbreviations: BM: bone marrow, PBSC: peripheral blood stem cell, Flu: fludarabine, ATG: anti-thymocyte globulin, Bu: busulfan, Alem: alemtuzumab, PT-Cy: post-transplant cyclophosphamide, TBI: total body irradiation, cGy: centigray, NA: not available

Table 2A

Summary of recent publications on Haploidentical hematopoietic cell transplant for sickle cell disease (2017–2022)

Reference	Size	Median Age years (range)	Graft Source	Conditioning Regimen	Median follow-up, months (range)	GVHD	Graft Failure	EFS	OS
Gilman et al. 2017	8	16 (8–23)	ex vivo CD34+ cell selected CD3+ depleted PBSC	ATG/Flu/Thio/Mel	21.5 (9.9–60)	25% acute, 13% chronic	13%	100%	87%
Frangoul et al. 2018	4	14(12–23)	BM/PBSC	ATG/Thio/Flu Cy/TBI 200 cGy/PT-Cy	16 (13–34)	100% acute, 0% chronic	0%	100%	100%
Pawlowska et al 2018	4	19 (13–23)	BM/PBSC	ATG/Flu/Bu/PT-Cy	9 (5–11)	25% acute, 75% chronic	0%	100%	100%
*Eapen et al 2019	137	19 (13–27)	BM/PBSC	varied	25 (12–48)	8.7% acute, 16% chronic	26%	67.2%	90.5%
Cairo et al. 2020	19	13(3–20)	PBSC	ATG/Flu/Cy/Thio/Bu/TBI 500 cGy	46.3 (1.9–73.3)	5% acute, 5% chronic	0%	84%	84%
Foell al 2020	25	13(3–31)	CD3+/CD19+ or TCR αβ/CD19+ depleted PBSC	ATG/Flu/Thio/Treo	20.0 (NR)	28% acute, 16% chronic	8%	100%	88%
*Gluckman et al 2020	71	9.3 (2–43)	BM/PBSC	varied	38 (2–154)	23% acute, 23% chronic	16%	62%	88%
Jaiswal et al 2020	5	8 (3–19)	PBSC	ATG/Flu/Treo/Mel/PT-Cy & Aba	28 (13–54)	0% acute, 0% chronic	0%	100%	100%
Kharya et. al 2021	25	7 (1–27)	PBSC	(Flu/Cy/Dex)/ATG/Flu/Cy/Thio/Bu/TBI 200 cGy//PT-Cy,	15.9 (6.5–26.3)	20% acute, 12% chronic	0%	88%	88%

* Registry studies, data include cases reported in the individual series.

Abbreviations: BM: bone marrow, PBSC: peripheral blood stem cell, Treo, treosulfan, Thio thiotepa, Flu: fludarabine, ATG: anti-thymocyte globulin, Bu: busulfan, Alem: alemtuzumab, Cy: cyclophosphamide, TBI: total body irradiation, cGY: centigray, Mel: melphalan, PT-Cy: post-transplant cyclophosphamide Aba: abatacept, Dex: dexamethasone NR: not reported

Table 2B

Summary of recent publications on haploidentical allogeneic cell transplant for sickle cell disease (2017–2022)

Adults									
Reference	Size	Median Age (range) yr	Graft Source	Conditioning Regimen	Median follow up, months (range)	GVHD	GRAFT Failure	EFS	OS
Fitzhugh et al 2017 [*]	12	36 (20–56)	PBSC	Alem/TBI 400 cGy PT-Cy	38.0 (8.1–73.91)	8.3% acute, 8.3% chronic	17%	50%	92%
Saraf et al. 2018	8	28 (20–38)	PBSC	ATG/Flu/Cy/300 cGy TBI/PT-Cy	16.8 (12 – 30.6)	28% acute, 16% chronic	13%	75%	87%
Bolanos-Meade et al 2019	12	26 (6–31)	BM	ATG/Flu/Cy/TBI 400 cGy PT-Cy	23.2 (11.7–42.5)	25% acute, 8% chronic	8%	83%	100%
de la Fuente et al 2019	15	20 (7–40)	BM	ATG/Flu/Cy/ATG/Thio/TBI 200 cGy/PT-Cy	18.0 (5.1–43.6)	33% acute, 7% chronic	7%	93%	100%

^{*} Results of the third cohort are presented.

Abbreviations: BM: bone marrow, PBSC: peripheral blood stem cell, Thio thiotepa, Flu: fludarabine, ATG: antithymocyte globulin, Alem: alemtuzumab, TBI: total body irradiation, cGy: centigray, Cy: cyclophosphamide, PT-Cy: post-transplant cyclophosphamide

Table 3A

Summary of clinical trials of recruiting and not yet recruiting studies for HLA Haploidentical and Matched Sibling Donor HCT

Recruiting	Identifier/ Location	Study Title	Age Range (years)	Participant Number	Phase	Study Goal
HLA Matched Related D						
Pediatrics	NCT03214354/ Calgary	A Phase II Pilot Study of Nonmyeloablative Conditioning Hematopoietic Stem Cell Transplantation in Children With Sickle Cell Disease Wh+C7:H14o Have a Matched Related Major ABO-Incompatible Donor (Sickle-AID)	1 Year to 19 Years	12	2	Safety and efficacy of NMA conditioning for matched related major ABO-incompatible donor.
	NCT04018937/ Emory	Early HLA Matched Sibling Hematopoietic Stem Cell Transplantation for Children With Sickle Cell Disease: A Sickle Transplant Advocacy and Research Alliance (STAR) Trial	2 Years to 13 Years	58	2	Safety and efficacy of fludarabine, alemtuzumab and melphalan (FAM) conditioning in pediatrics.
	NCT03587272/ DC	Minimizing Toxicity in HLA-Identical Related Donor Transplantation for Children With Sickle Cell Disease	2 Years to 25 Years	30	2	Decrease toxicity while achieving a high cure rate for children using alemtuzumab, low dose total-body irradiation, and sirolimus
	NCT01499888/ Chicago	Ph I/II Study of Allogeneic SCT for Clinically Aggressive SCD	16 Years to 60 Years	15	1 / 2	Use of immune-suppressive agents and low-dose TBI in patients not candidates for or experienced complications from hydroxyurea therapy.
	NCT02105766/ NIH	Nonmyeloablative Peripheral Blood Mobilized Hematopoietic Precursor Cell Transplantation for Sickle Cell Disease and Beta-Thalassemia in Individuals With Higher Risk of Transplant Failure	4 Years and older	162	2	To see if low dose radiation (300 cGy), oral cyclophosphamide, pentostatin, and sirolimus help to better accept donor stem cells.
Children and Adults	NCT03421756/ Pittsburgh	A Pilot Study Evaluating the Efficacy of Non-Myeloablative Matched Related Donor Peripheral Blood Stem Cell Transplant in Patients With Severe Sickle Cell Disease	18 Years and older	12	1	MRD allogeneic SCT in adults with severe sickle cell disease using alemtuzumab.
	NCT00061568/ NIH	Nonmyeloablative Allogeneic Peripheral Blood Mobilized Hematopoietic Precursor Cell Transplantation For Severe Congenital Anemias Including Sickle Cell Disease (SCD) and Beta-Thalassemia	2 Years and older	150	1/2.	Low dose radiation, alemtuzumab and sirolimus as a strategy to provide clinical remission with a lower risk of GVHD development
	NCT05249452/ Amsterdam	Adding Azathioprine/ Hydroxyurea Preconditioning to Alemtuzumab/TBI to Reduce Risk of Graft Failure in Matched Sibling Donor Allogeneic HSCT in Adult Sickle Cell Patients	16 Years to 60 Years	20	N/A	Investigate whether 3-month long preconditioning with azathioprine and alemtuzumab/TBI improves disease-free survival and donor chimerism

Recruiting						
	Identifier/ Location	Study Title	Age Range (years)	Participant Number	Phase	Study Goal
	Identifier	Study Title	Age range (yr)	Participant Number	Phase	Study Goal
HLA Haploidentical						
Pediatric	NCT04362293/S t. Jude	Reduced Intensity Related Donor Peripheral Blood Derived Hematopoietic Progenitor Cell Transplantation for Patients With Severe SCD	2 Years to 25 Years	40	2	RIC of alemtuzumab, thiotepa and low dose total body irradiation and pre-conditioning of hydroxyurea and azathioprine to reduce the risk of graft rejection.
	NCT04207320/ Chicago	Hematopoietic Stem Cell Transplantation for Patients With Severe Sickle Cell Disease Using Myeloablative Conditioning and $\alpha\beta+$ T-cell Depleted Hematopoietic Stem Cells From Partially Matched Familial Donors	2 Years to 25 Years	38	N/A	Safety of haploidentical HSCT using $\alpha\beta+$ T-cell depletion for children and adolescents with severe SCD.
	NCT03367546/ Minnesota	Haploidentical Donor T-cell Replete Allogeneic Hematopoietic Cell Transplant Following Reducing Intensity Conditioning for Patients With Selected High Risk Non-Malignant Disease	up to 25 Years	20	2	Use of T-cell replete RIC Haplo HCT for individuals who lack a suitable HLA-matched sibling donor.
	NCT03279094/ City of Hope	A Pilot Study of Pre-transplant Immunosuppressive Therapy for Haploidentical Transplants in Patients With SCD	1 Year to 30 Years	18	1	Haploidentical donors and non-toxic, myeloablative regimen, with the goal of achieving consistent donor chimerism.
	NCT03240731/ Paris	BMT HLA Haploidentical After RIC and Prevention of GVHD Based on Post-transplant Cyclophosphamide Administration in Patients With Severe SCD	13 Years to 40 Years	16	2	RIC haploidentical marrow transplants and prevention of GVHD based on cyclophosphamide administration post-transplantation.
	NCT03263559/ Wisconsin	Haploidentical BMT in Sickle Cell Patients (BMTCTN1507)	5 Years to 45 Years	80	2	Use of pre-conditioning hydroxyurea with Thymoglobulin/Cyclophosphamide/Fludarabine/Thiotepa and post-transplant high-dose cyclophosphamide.
	NCT02757885/ Emory	Transplantation Using Reduced Intensity Approach for Patients With SCD From Mismatched Family Donors of Bone Marrow (TRANSFORM)	15 Years to 40 Years	15	2	Haploidentical SCT with hydroxyurea, fludarabine, thiotepa, anti-thymocyte globulin, radiation and cyclophosphamide.
	NCT02065596/ Cleveland	Hematopoietic Stem Cell Transplant for Sickle Cell Disease	18 Years to 65 Years	25	1/2.	Use of fludarabine to reduce graft rejection.
	NCT03077542/ NIH	Nonmyeloablative Haploidentical Peripheral Blood Mobilized Hematopoietic Precursor Cell Transplantation for Sickle Cell Disease	2 Years and older	93	1/2.	Decrease risk of GVHD with low radiation dose, Alemtuzumab, Sirolimus, Cyclophosphamide, and pentostatin.

Table 3B

Summary of clinical trials of recruiting and not yet recruiting studies for HLA Haploidentical and Matched Related Donor HCT

	Identifier	Study Title	Age range (yr)	Participant Number	Phase	Study Goal
HLA Haploidentical						
Children and Adults	NCT03653338/ Pittsburgh	T-Cell Depleted, Alternative Donor Transplant in Pediatric and Adult Patients With Severe Sickle Cell Disease (SCD) and Other Transfusion-Dependent Anemias	5 Years to 40 Years	5	1/2.	CD3/CD19 depletion of mismatched donor grafts in the setting of reduced intensity, immune-ablative conditioning.
	NCT03121001/ Chicago	A Phase II Study of HLA-Haploidentical Stem Cell Transplantation to Treat Clinically Aggressive Sickle Cell Disease	16 Years to 60 Years	50	2	HLA-haploidentical HSCT protocol using immunosuppressive agents and low-dose TBI for conditioning and post-transplant cyclophosphamide.
	NCT03249831/ City of Hope	Pilot Study to Evaluate the Safety and Feasibility of Induction of Mixed Chimerism in Sickle Cell Disease Patients With COH-MC-17: a Non-Myeloablative, Conditioning Regimen and CD4+ T-cell-depleted Haploidentical Hematopoietic Transplant	18 Years to 45 Years	6	1	Safety and feasibility of COH-MC-17 (cyclophosphamide, pentostatin and rabbit-anti-thymocyte globulin (ATG)) followed by a CD4+ T-cell-depleted Haplo HCT to induce mixed chimerism.
	NCT02675959/ NY	Safety and Efficacy of Prophylactic Defibrotide in Children, Adolescents, and Young Adults With Sickle Cell Disease or Beta Thalassemia Following MAC and Haploidentical Stem Cell Transplantation Utilizing CD34 Enrichment and T-Cell (CD3) Addback	6 Months to 34 Years	40	2	Follow-up trial to NYMC 526 (NCT01461837) to assess Defibrotide prophylaxis for haploidentical allogeneic SCT with CD34 enrichment and T-cell addback.
	NCT04201210/ Germany	A Phase II Stratified Trial to Assess Haploidentical T-depleted Stem Cell Transplantation in Patients With Sickle Cell Disease With no Available Sibling Donor	1 Year to 35 Years	212	2	Can an α/β depleted T-Haplo-HCT improve disease-free survival, adverse events and safety which is equivalent to a MSD HCT.
	NCT04776850/ Texas	Pre-Transplant Immunosuppression and Related Haploidentical Hematopoietic Cell Transplantation for Patients With Severe Hemoglobinopathies	2 Years to 30 Years	40	1	Pre-transplant immunosuppression (PTIS) to lower the risk of GVHD.

Table 3C

Summary of clinical trials of recruiting and not yet recruiting studies for HLA Haploidentical and Matched Sibling Donor HCT

Not yet recruiting						
Identifier	Study Title	Age range (yr)	Participant number	Phase	Study Goal	
NCT04046705/Paris	A Prospective Multicenter Trial Comparing Allogeneic Matched Related HSCT After a RIC Regimen, With Standard of Care in Adolescents and Adults With Severe SCD	15 Years to 45 Years	78	3	Compare NMA MSD HCT versus no HSCT (for patients lacking MSD).	
NCT04099966/NY	Allo SCT for Malignant and Non-malignant Hematologic Diseases Utilizing Alpha/Beta T Cell and CD19+ B Cell Depletion	up to 30 Years	20	2	Utilizing α/β CD3+/CD19+ cell depletion to decrease the incidence of GVHD.	

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