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Stem cell transplantation in sickle cell disease: therapeutic potential and challenges faced

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Abstract

Introduction: Sickle cell disease (SCD) is the most common inherited hemoglobinopathy worldwide, and is a life limiting disease with limited therapeutic options to reduce disease severity. Despite being a monogenic disorder, the clinical phenotypes of SCD are variable, with few reliable predictors of disease severity easily identifying patients where the benefits of curative therapy outweigh the risks. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative option, though significant advances in gene therapy raise the promise for additional curative methods.

Areas Covered: Allogeneic transplantation in SCD has evolved and improved over the last two decades, now offering a standard of care curative option using an HLA-matched sibling donor. Many of the seminal transplantation studies are reviewed here, demonstrating how initial failures and successes have influenced and led to current HSCT strategies. Such strategies aim to overcome setbacks and limitations, and focus on conditioning regimens, immune suppression methods, the use alternative donor sources, and gene therapy approaches.

Expert Commentary: SCD is a curable disease. Each dedicated effort to refine transplantation methods, expand the donor pool, and bring gene therapy models to fruition will make enormous impacts reducing disease burden and improving outcomes and quality of life for patients with SCD.

Keywords

allogeneic transplantation; autologous transplantation; gene therapy; hematopoietic stem cell transplantation; sickle cell disease

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1. Introduction

Sickle cell disease (SCD) encompasses a group of disorders characterized by a single point mutation in the beta globin gene. Whether inherited in a homozygous state or with another abnormal beta-globin gene, the substitution of glutamic acid by valine in the sixth codon on chromosome 11 produces an abnormal hemoglobin S (Hb S) which polymerizes in the deoxygenated state and produces abnormal red blood cells (RBCs) with limited deformability, lifespan, and function. This single monogenic change is responsible for many downstream effects and the numerous devastating clinical complications of SCD including chronic anemia, chronic inflammation, vasoocclusion and severe pain, stroke, organ failure, and early mortality [1].

SCD is a global health problem with a need for cure. Approximately 5% of the world's population carries trait genes for hemoglobin disorders, mainly SCD and thalassemia [2]. Approximately 300,000 babies with severe hemoglobin disorders are born each year, though this number is estimated to rise to over 400,000 by 2050 [3]. In the United States (US), SCD is a public health concern with high health care costs [4], affecting approximately 100,000 Americans who have less access to comprehensive care teams than people with other genetic disorders like hemophilia and cystic fibrosis where specialized treatment centers establish patient registries to monitor outcomes and evaluate the effectiveness of treatment protocols [5]. Despite significant reductions in excess early childhood mortality through newborn screening, penicillin prophylaxis, and vaccinations, the two mainstay treatments for SCD, blood transfusions and hydroxyurea (HU), are not free of side effects, and do not fully eliminate the consequences of the disease. Hematopoietic stem cell transplantation (HSCT) offers patients a chance for cure, and along with the promise of gene therapy for SCD, is a way to reduce disease burden, improve outcomes and quality of life for patients with SCD, and significantly reduce health care costs over the long term.

Since the first HSCT in 1984 for a pediatric patient with SCD and acute myelogenous leukemia, thousands of patients have successfully undergone bone marrow (BM) HSCT with an HLA-identical sibling donor, with greater than 90% of all patients cured of SCD [6–9]. Whether using a myeloablative or non-myeloablative preparative regimen, HSCT using an HLA-identical sibling donor should no longer be considered experimental. Unfortunately, less than 15% of patients with SCD in the US have an appropriately matched donor [8] for which matched unrelated donor (MUD) transplantation, umbilical cord blood transplantation (UCBT), and haploidentical transplantation may offer more patients the chance for cure, though high rates of complications currently limit the broad use of these therapies.

As the options and outcomes improve for allogeneic transplantation in SCD, gene therapy for the cure of SCD is simultaneously becoming a realistic option for patients. Whereas allogeneic transplantation is limited by donor availability, the potential for morbidity and mortality from transplant conditioning, graft-vs-host disease (GVHD), and graft rejection, gene therapy either by gene addition or gene modification targeting autologous hematopoietic stem cells (HSCs) offers the premise of a cure for SCD that is available to all patients, and is currently being investigated in multiple clinical trials.

2. Indications for HSCT

Interventions such as newborn screening, penicillin prophylaxis, primary stroke prevention, and HU treatment have significantly reduced infant and pediatric mortality in both developed and underdeveloped countries [10–11]. Although more than 94% of children with SCD in well-resourced countries now survive until the age of 18 years, chronic complications, reduced quality of life, and mortality are still significant once patients reach adulthood. Curing SCD is therefore an important and necessary medical goal. Offering HSCT to patients must be made in the context of risk vs. benefit to the patient, with suitability of the donor match and pre-HSCT illness severity contributing to this risk/benefit balance. Additionally, any medical treatment, including HSCT or gene therapy, must uphold the ethical principles of nonmaleficence, beneficence, respect for autonomy, and justice [12].

Despite being a monogenic disorder, the clinical phenotypes of SCD are extremely variable. There are few reliable predictors of disease severity that would easily elucidate those patients whose risk of disease sequelae clearly outweigh the risk of potential morbidity and mortality from HSCT. Given its investigational nature, the first large multicenter trial investigating HSCT for SCD selected patients who appeared to have a high risk of severe morbidity and early death [6]. Despite reporting a high overall survival (OS) and event-free survival (EFS) at four years of 91% and 73% respectively, the authors acknowledged that the “optimal timing of marrow transplantation in the course of sickle cell anemia remains uncertain, in part because of the unpredictable nature of the disease”. Over the last two decades since this trial there have been significant improvements in preparative regimens, supportive care, and management of complications for which an expert panel was convened to provide consensus-based recommendations on the indications for HSCT and transplant management [13]. Noting disease free survival (DFS) of 95% at 3 years with an HLA-matched sibling donor, an EFS being significantly better in patients transplanted before developing SCD-related organ damage, and treatment related mortality (TRM) that increase with age, the panel recommends that “young patients with symptomatic SCD who have an HLA-matched sibling donor should be transplanted as early as possible” [10, 15–16]. For those who do not meet these criteria, “SCT from unrelated BM or CB donors should only be considered in the presence of at least one of the indications suggested by Walters et al [6] and should be performed only in the context of controlled trials in experienced centers”.

Symptomatic SCD is not clearly defined and thus there are no universal, widely adopted indications for HSCT. The presence of CNS disease, however, is an undisputed indication for HSCT given as many as 20% of children with previous strokes and cerebral vasculopathy may experience second overt strokes within 5 years, and up to 45% may experience progressive cerebral infarcts despite adequate transfusion therapy [18–19]. Recurrent vasoocclusive crisis (VOC) despite HU, recurrent acute chest syndrome (ACS), osteonecrosis, sickle nephropathy, red cell alloimmunization, pulmonary hypertension, and recurrent splenic sequestration encompass other “severe” disease complications that should be considered indications for HSCT [20], yet most of these reflect expert opinion due to the absence of a sound evidence base. Given lack of universal indications, centers may adopt their own guidelines and may include poor response to HU and parent or patient preference

as additional considerations. Exclusionary criteria for studies are narrowing as treatment options and supportive care expands, but generally include a Karnofsky or Lansky functional performance score <50–70, acute hepatitis or evidence of moderate or severe portal fibrosis or cirrhosis on biopsy, severe renal impairment, severe cardiac disease, stage III or IV sickle lung disease, demonstrated lack of compliance with medical care, seropositivity for the human immunodeficiency virus, or uncontrolled infections.

Though HLA-identical HSCT should be considered the standard of care for those with symptomatic SCD and an HLA-matched sibling donor, there is an underutilization of this curative therapy for patients. Given a 10–15% chance of having an HLA-identical donor in the US, there should be roughly 10,000 patients who are eligible for transplantation just in the US alone, yet only around 1,200 patients have been transplanted according to the Centre for International Blood and Marrow Transplant Research (CIBMTR) as of 2014 [19] despite patient willingness to consider HSCT despite known morbidity and mortality [21]. Whereas HSCT has the best outcome when performed prior to irreversible organ damage, the inability to predict disease severity prior to overt clinical symptoms or organ damage, and concern for patient autonomy in the pediatric setting has limited patient referral and provider comfort with offering or recommending this curative therapy. The importance of a shared decision-making model among providers, patients, and their families is imperative to ensure acceptable considerations are addressed regarding the various potential risks and benefits of choosing to either decline or undergo HSCT [12]. Where there may be consensus to offer HSCT to those who have experienced an overt stroke, and a consensus not to offer HSCT for patients with milder disease such as hereditary persistence of fetal hemoglobin or HbS β + disease, other disease criteria are less straightforward and therefore any limitations of acceptability can only be made by an individual patient or their parents after thoughtful and informed discussion. Such discussions should center around the inability to precisely predict SCD severity, the cumulative organ damage from SCD, harm that may occur by not electively performing early HSCT as outcomes worsen with age compared to the low risk of major complications from HSCT. Such complications from HSCT include death or significant organ toxicity such as endocrine dysfunction and infertility, secondary malignancy, and the substitution of one disease (SCD) for another (GVHD).

3. HLA-identical sibling allogeneic hematopoietic stem cell transplantation

After 20 years of clinical experience, HSCT should be considered standard of care when a patient has an indication and an HLA-identical sibling donor. The first successful cure of SCD after HSCT was reported in a single pediatric patient in 1984 who had SCD and coexisting acute myeloid leukemia [22]. Over the next three decades between 1986 and 2013, over 1,000 patients have received an HLA-identical sibling HSCT with a 5-year EFS and OS of 91.4% and 92.9%, respectively [9]. EFS is lower with increasing age at transplantation and higher for transplantations performed after 2006 given improvements in preparative regimens, supportive care, and management of complications.

3.1 Myeloablative conditioning

Initial trials in HSCT for SCD included myeloablative conditioning regimens with BM as the HSC source [6, 23–24]. In the first large multicenter trial [6], 22 pediatric patients with symptomatic SCD were treated with myeloablative doses of busulfan (BU) in combination with highly immunosuppressive doses of cyclophosphamide (CY) (similar to European studies, [23–24]) and T cell depletion with antithymocyte globulin (ATG) or Alemtuzumab. A combination of methotrexate and cyclosporine or cyclosporine and prednisone was used as GVHD prophylaxis. EFS and OS at 4 years were reported at 73% and 91% respectively, with most of the failures occurring as a consequence of graft rejection/disease recurrence.

Subsequent studies using similar preparative regimens (+/- Fludarabine [25, 26], +/- HU [27]) with larger cohorts have published EFS ranging 82–100% and OS ranging 91–100% (Table 1) [6, 8, 25–32]. EFS was improved further with the addition of ATG [27, 28], noting an improvement in the 5-year EFS from 86% to 95% in patients treated after 2000 with the addition of ATG. EFS was also noted to be higher in patients who received HU prior to HSCT, with an EFS at 8y of 97.1% which was significantly higher than EFS in those who did not receive HU prior to HSCT ($p < 0.001$) [27, 33]. The overall rates of acute and chronic GVHD utilizing a cyclosporine based immunosuppressive regimen range between 10–22%, though GVHD was a main cause of treatment related mortality (TRM) in several studies [25, 28, 29, 32]. One study noted two groups of patients divided based on their access to optimal care. The first group consisted of patients who were permanent residents of a European country who met the traditional symptomatic SCD inclusion criteria as previously defined [6]. The second group consisted of asymptomatic patients (median age 2y) who were transplanted at a younger age since their family was returning to Africa where medical care was not considered to be optimal. Noted differences between the groups included a higher OS (88% vs. 100% in group 2), EFS (76% vs. 93% in group 2), DFS (80% vs. 93%), lower rejection (25% vs. 7% in group 2, $p < 0.001$), and lower GVHD (none in group 2), showing a clear advantage of early intervention.

In addition to improved outcomes noted for younger patients without severe disease, three important lessons were learned over the course of these initial studies. First, the addition of ATG decreases the risk of graft rejection from 22.6% to 3% and should be considered as standard of care in HSCT myeloablative preparative regimens [27, 28]. Second, there is an increased incidence of neurologic complications including seizures and fatal intracranial hemorrhage in this patient population for which anticonvulsant prophylaxis and strict platelet, hemoglobin, blood pressure, and magnesium parameters are warranted [34]. Third, stable mixed chimerism with a reduction rather than an elimination of hemoglobin S is sufficient to reverse the SCD phenotype as erythropoiesis by a minority of engrafted donor cells can lead to a majority of circulating normal erythrocytes with a survival advantage over short-lived sickle RBCs. This latter lesson paved the way for less toxic, non-myeloablative conditioning regimens.

3.2 Non-myeloablative Conditioning

Results from studies utilizing a myeloablative preparative regimen demonstrated that patients with mixed chimerism had sufficient donor hemoglobin to overcome the SCD

phenotype, and therefore less toxic, non-myeloablative conditioning may be an efficacious and safer option. Myeloablative therapy is limited by the short and long-term toxicities of BU/CY, including but not limited by TRM and morbidity including infertility and gonadal failure, secondary malignancy, and more severe organ toxicity in patients who have impaired organ function pre-HSCT or have been exposed to multiple RBC transfusion prior to HSCT. By using reduced toxicity with immunomodulatory conditioning, engraftment may still be achieved and allow older adults who have accumulated end-organ damage, those refractory to HU, or those who have developed severe-alloimmunization precluding RBC transfusion to be eligible for this curative therapy.

Early trials with non-myeloablative conditioning were notable for high rates of graft failure and disease recurrence (Table 2)[35–37]. The cyclosporine based immunosuppressive regimen continued to show GVHD, and once weaned, patients often rejected their grafts [36]. Based on concerns for calcineurin induced neurologic complications and worsening of renal function, and on the basis of a novel mechanism for inducing immunologic tolerance, Hsieh et al substituted cyclosporine with sirolimus (formerly known as rapamycin) in a regiment employing low dose total body irradiation (TBI) and alemtuzumab and demonstrated minimal rejection and no acute or chronic GVHD [7, 38]. Unlike calcineurin inhibitors such as cyclosporine that inhibit the activation and secretion of IL-2, sirolimus inhibits the secondary IL-2 receptor dependent signal transduction required for T-cell proliferation. Thus activated T cells cannot proliferate and become anergic, promoting T-cell tolerance and therefore minimize the risk of GVHD [39]. Furthermore, given previous reports of veno-occlusive disease from alkylating agents such as BU and CY [29, 31], the novel preparative regimen of TBI at 300 cGy with alemtuzumab for T cell depletion was chosen given previous results with low dose radiation [40] and improved infusional tolerance and superior prophylaxis against GVHD of alemtuzumab over ATG in patients with SCD [41–42]. Additionally, Alemtuzumab remains detectable for several weeks and further deletes alloreactive T cells during subsequent donor engraftment and initial immune reconstitution. Results from these trials showed older patients being successfully transplanted with GCSF mobilized peripheral blood stem cells (PBSCs) with an EFS and OS of 87% and 97% respectively, a 13% rejection rate, no TRM, and no acute or chronic GVHD. Additionally, the majority of engrafted patients have discontinued immunosuppression medication with continued stable donor chimerism and no GHVD. These results have been confirmed at another center in 13 subjects treated with the identical protocol, showing an OS and EFS of 100% and 93% respectively, and no TRM or acute or chronic GVHD [43]. One patient had secondary graft failure due to sirolimus non-compliance.

In other smaller series, patients have received various conditioning regimens including low dose BU, varying doses of TBI, fludarabine, melphalan, and/or ATG/alemtuzumab [44–46]. All three studies show an OS of 100%, with minimal graft rejection and minimal to no acute or chronic GVHD. Based on nearly 1,000 patients who received a HSCT (873 myeloablative, 125 non-myeloablative), there was no difference in EFS or OS based on preparative regimen (myeloablative vs. non-myeloablative) further supporting the investigation of non-myeloablative treatment regimens for a potentially safer and broader range of patients with SCD [9].

4. Alternative Donor Sources

Given the lack of eligible patients with SCD who have an HLA-matched sibling, understanding and maximizing alternative donor sources is critical for offering a chance for a cure of SCD. Unrelated BM or UCB expands the donor pool and have successfully been used as an alternative allogeneic donor source for pediatric malignant and non-malignant disorders including genetic, hematologic, and immunologic disorders [47]. Data regarding the use of unrelated BM or UCB donors in HSCT for patients with SCD remains limited however, particularly given less common, more diverse haplotypes in Africans than the white population, and an underrepresentation of ethnic minorities in the BM donor registries worldwide [48–49]. According to the expert panel, “due to the lack of matched donors in the registries there are no firm data on outcome of HSCT from unrelated donors for SCD, and, therefore, the advantages and disadvantages of this option cannot be adequately addressed” [13]. HSCT from unrelated BM or CB is therefore recommended to be considered for severe disease and done only on a clinical trial at experienced centers.

4.1 Umbilical cord blood transplantation

Lower rates of GVHD and TRM were noted in several studies investigating myeloablative conditioning for HLA-identical sibling HSCT who used CB as the donor source [28, 50]. UCB is a rich source of hematopoietic stem and progenitor cells with extensive proliferative capacity that has the advantage of lowered risk of GVHD compared to marrow transplantation [51]. This lowered risk of GVHD is balanced by a higher rate of graft rejection, poor immune reconstitution, and a prolonged period of hematologic recovery where there is a high risk for infection [52]. Many trials using primarily unrelated UCB as the donor source are limited by small numbers of patients treated, and show high rates of graft rejection and infection (Table 3)[53–57]. The Sickle Cell Unrelated Donor Transplant (SCURT) trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0601) is a phase II study of the toxicity and efficacy of unrelated donor hematopoietic cell transplantation in children with severe SCD using a reduced intensity conditioning regimen (NCT00745420). The UCB arm of this trial was suspended due to high incidence of graft rejection (63%)[57]. Although initially disappointing, these studies revealed that the use of methotrexate for GVHD prophylaxis is associated with a greater risk of treatment failure [52], and DFS can be improved with CB units containing total nucleated cell dose $>5 \times 10^7/\text{kg}$ [56].

As opposed to unrelated donors, there are encouraging data when related, HLA-identical sibling CB donor sources are used, confirming the importance of an HLA-matched sibling for success regardless of donor cell source. The most recent update comparing HLA-identical sibling marrow vs. UCB transplant outcomes for 485 recipient cases with thalassemia major or SCD was published from the CIBMTR and European Group for Blood and Marrow Transplantation (EBMT) registry data from US and European transplant centers [50]. One hundred sixty patients with SCD who underwent HSCT were included in this analysis, of which 30 patients received CB as their donor source. Compared to those who received BM, those who received CB had delayed neutrophil recovery (BM = 19 days, range 8–56 vs. CB = 23 days, range 9–60, $p=0.002$) but less acute and chronic GVHD

(acute GVHD BM = 21% vs. CB = 11%, $p=0.04$; chronic BM = 12% vs. CB = 7%, $p=0.12$). None of the patients who received CB developed extensive chronic GVHD or died of GVHD related complications. It must be noted, however, that those who received CB were younger than those who received BM [combined thalassemia and SCD median age 5.9 (CB) vs. 8.1 (BM), $p=0.02$], and therefore cannot exclude that the younger age of CBT recipients could have contributed to the lower incidence and severity of GVHD in comparison with BM recipients. The 6-year OS for all patients was 95 and 97% for BM and CB HSCT, respectively ($p=0.92$), and the 6y DFS for patients with SCD was 92% and 90%, respectively. Two patients who received CB had primary graft failure and were successfully retransplanted from the same donor, though source was not identified. Six patients had secondary graft failure at a median time of 151 days (range 51–202 days). In this study, the cell dose infused did not influence outcome of patients given CB, and there was no difference in the cumulative incidence of primary graft failure.

4.2 Unrelated Donor

The current experience of unrelated donor BM or CB HSCT for SCD is quite limited, with overall discouraging results. There are more published results for unrelated donor CB HSCT as previously mentioned [54–57], with disappointing rates of graft rejection and TRM. Data from the BM arm of the SCURT trial was recently published, showing an EFS and OS of 69% and 79% respectively, and a TRM of 28% of which there were 7 GVHD related deaths with a 62% rate of chronic GVHD [58]. The authors concluded that although the 1-year EFS met the pre-specified target of 75%, this regimen cannot be considered sufficiently safe for widespread adoption without modifications to achieve more effective GVHD prophylaxis.

The Bone Marrow Transplantation in Young Adults With Severe Sickle Cell Disease (STRIDE) trial includes patients who have a related or an unrelated HLA-matched donor, and is evaluating the safety and feasibility of unrelated donor HSCT in adults with SCD (NCT01565616). Preliminary results published after 1 year show similar results to previous trials [2, 38, 45] using reduced intensity conditioning, though data from the 5 patients with SCD who received an unrelated HSCT are not separated from the 17 patients with a related donor in the published results (Table 3)[59]. The authors report an EFS and OS of 95%, no graft rejection, minimal GVHD, and one death from ICH related to PRES. If sustained long-term after HSCT and confirmed in a larger comparative trial, this approach would broaden the availability and application of transplantation for adults with severe SCD.

Together these data present an unclear picture for the success of unrelated BM or CB transplantation in patients with SCD. Whereas successful outcomes have been reported, the ideal condition of the patient and treatment regimen have yet to be established. Given small successes, it is likely that better conditioning regimens, improved and refined donor/recipient HLA-matching, higher cell dose for CB, identification of anti-HLA antibodies, and improved effectiveness of GVHD prophylaxis is required to ensure acceptable outcomes.

5. Haploidentical transplantation

Haploidentical transplantation promises an expanded donor pool of biological parents, biological children, full or half siblings, or even extended family donors to patients with

SCD who otherwise satisfy eligibility requirements for HSCT but lack a suitable matched related or unrelated donor. An HLA-haploidentical donor shares exactly one HLA haplotype with the recipient but is mismatched for a variable number of HLA genes on the unshared haplotype. The major challenge of HLA-haploidentical HSCT is therefore the bi-directional alloreactivity leading to high incidences of graft rejection and GVHD. Unlike patients with hematologic malignancies who are pre-treated with chemotherapy and irradiation, patients with SCD may have a higher risk of graft rejection due to an intact and robust immune system, a lifetime of anemia and chronic inflammation, and higher incidence of alloimmunization. To broaden the availability of transplantation to a much larger fraction of patients, improving engraftment without increasing GVHD is the goal, particularly as there is no benefit of graft-vs-tumor effect in nonmalignant diseases, and the substitution of one chronic, debilitating disease for another is generally unacceptable.

Novel strategies to lower the risk of GVHD in haploidentical protocols are focused on T cell depletion methods, and include in vivo post HSCT CY and ex vivo infusion of a CD34 positively selected donor grafts.

In vivo, high-dose CY given on days 3 and 4 post HSCT is highly cytotoxic to both donor and recipient proliferating, alloreactive T cells [60], yet spares HSCs secondary to their high levels of the enzyme, aldehyde dehydrogenase, responsible for metabolizing the drug [61]. GVHD prophylaxis with high-dose CY has proven effective with very low rates of both acute and chronic GVHD after HLA-haploidentical related HSCT (Table 4)[62]. For those patients with evidence of engraftment, this approach showed no acute or chronic GVHD. The regimen was well tolerated with limited serious toxicities, with an OS of 100%. Despite these advantages, rejection was high at around 50% and remains an important obstacle for the haploidentical HSCT model. Preliminary evidence suggests the addition of thiopeta in the preparative regimen may improve donor engraftment without increasing morbidity or mortality [63], and is currently being investigated in a phase II clinical trial (NCT03240731).

The ex-vivo model of CD3+ depleted, CD34+ selected grafts avoids the potential toxicities of in vivo depletion agents but comes with the drawbacks of a labor-intensive process and poor immune reconstitution after the removal of desirable immune cells such as natural killer cells and $\gamma\delta$ T cells. One single center has published results from 8 patients with SCD who underwent haploidentical HSCT based on grafts with CD3+ depletion and CD34+ selection [64], reporting high rates of acute and chronic GVHD (40% and 75%, respectively) of which two patients died from complications related to chronic GVHD. Furthermore, patients who received high doses of CD3+ T cells or donor lymphocyte infusions were at significant risk for increased mortality. The authors concluded that although the small number of patients in both studies [62, 64] limit conclusive results, the findings suggest that a preparative regimen with post-transplantation CY may be more effective than T cell depletion in preventing GVHD.

Current and future work to optimize the haploidentical model includes trials investigating pre-transplant immunosuppressive therapy (NCT03279094), the use of autologous mesenchymal stem cells to modulate recipient T-cell immune responses and promote engraftment (NCT03298399), utilizing a non-myeloablative regimen with a CD34+ selected

graft (NCT02165007), a CD4+ T cell depleted graft (NCT03249831) or peripheral blood mobilized stem cells (PBSCs)(NCT03077542). Other active and recruiting trials for HSCT in patients with SCD as listed on [ClinicalTrials.gov](https://clinicaltrials.gov) as of December 2017, including gene therapy trials, are listed in Table 5.

6. Long-term effects post transplantation

A consensus summary reviewing long term follow-up results and identifying research priorities in late effects after HSCT in children with SCD and thalassemia [65] has now been followed up with comprehensive late effects screening guidelines [66]. In general, patients with stable donor engraftment after HSCT do not experience sickle-related complications after HSCT and may see stabilization or even improvement in end organ pathology, yet the risk of infertility remains a significant area of concern for both patients and their families [6–7, 26–28, 38, 67].

A recent analysis of the long-term effects of 59 children with SCD who underwent HSCT between 1991–2000 strongly suggests that in addition to a lack of painful or other clinical events related to SCD in patients with durable engraftment of donor cells, most individuals are also protected from subclinical progression of end-organ pulmonary and CNS dysfunction that is associated with sickle related pathophysiology [67]. Data suggests that children with stroke and successful engraftment are protected from a second stroke or further silent ischemic lesions after HSCT, including those with progressive cerebrovascular disease [28, 67]. Patients with elevated arterial cerebral velocities before HSCT have conditional or normal values afterwards, and often the brain magnetic resonance imaging (MRI) exams demonstrate stable or improved appearance post-HSCT [7–8, 27–28, 38, 67]. In those with more severe baseline MRI findings however, there may be clinically silent parenchymal and vascular changes on MRI after HSCT despite 100% donor chimerism and normal erythropoiesis [64, 68]. In a prospective study of 9 children, persistent MRI changes occurred in 5, parenchymal lesions occurred in zero of 2 patients without prior lacunae or infarcts and in all 7 with prior lacunae or infarcts ($p=0.0278$) over a period of 7 months to 6.5 years post-HSCT [68]. Despite these MRI changes, cognitive function remained stable over 3 years after HSCT, which is in contrast to one study of adults post-HSCT where a high proportion developed white matter lesions, atrophy, cognitive deficits, or neurological abnormalities, possibly related to chronic GVHD [69]. Overall, post-HSCT MRI findings tend to show a majority of patients have stable CNS disease with improvement in some and potential worsening in a small proportion of patients [70].

For those with recurrent ACS or pulmonary hypertension, pulmonary function tests are often stable or improved [8, 67], though this is not seen in all patients [64]. In adults transplanted with a non-myeloablative regimen, mean tricuspid regurgitant velocity improved from 2.84 m/s (95% CI 2.71–2.99) before HSCT to 2.33 (95% CI, 2.14–2.51) 3 years after HSCT ($P = .01$ for tricuspid regurgitant velocity 2.6–2.9 m/s, and $P < .001$ for tricuspid regurgitant velocity ≥ 3 m/s, mixed-model regression)[7]. Though mild tricuspid regurgitation has been reported post-HSCT, jet velocities are normal with no clinical impact on cardiac function [64]. As for other measurable outcomes, growth is overall unchanged, whereas weight does improve [27, 28]. Splenic reticuloendothelial dysfunction may improve [28, 43, 71] and

penicillin prophylaxis can be stopped in the absence of GVHD or splenectomy [30]. Normal fatty replacement of bone occurs in patients with a history of osteonecrosis [28] though others report no improvement on X-ray [30]. In patients with sickle cell nephropathy and proteinuria, there is no worsening of the previously established decline in renal function [7, 38] and in fact may show improvement [46]. Most importantly, however, patients report a markedly improved quality of life after successful HSCT [43, 72]. In the majority of cases it is possible to discontinue immunosuppressive medication 6–12 months after HSCT with a return to normal school and work life. Mean annual hospitalization rate declines from 3.23 (95% CI, 1.83–4.63) the year before HSCT to 0.11 (95% CI, 0.04–0.19) the third year after transplant, and a majority of patients are able to successfully wean from narcotics [7]. Successful HSCT leads to resolution of pain in the large majority of SCD patients, however there is a subgroup of patients who continue to require opioids post-HSCT. While there is a significant reduction in the prescription of both short- and long-acting opioids post HSCT (91% to 40% for short-acting and 40% to 15% for long-acting opioids), 40% of patients report persistent pain requiring opioids, with pain outcomes post-HSCT potentially influenced by pre-HSCT pain characteristics including higher pain burden (higher pain admissions and higher pain intensity ratings), more symptoms of anxiety, and more probable use of long-acting opioids pre-HSCT [73]. Despite continued use of opioids in these patients, however, there is a significant improvement in pain intensity, pain impact, satisfaction with social role, and physical function following HSCT.

The long-term limitations surrounding HSCT for patients often centers around gonadal failure and the risk of infertility. This risk depends on several factors, including pre-transplant hydroxyurea use, transfusion associated iron overload, or recurrent priapism, in addition to the effects of myeloablative and gonadotoxic chemotherapeutic agents, the inclusion of radiation, and the stage of pubertal development at the time of HSCT [67, 74]. Low testosterone and abnormal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were reported in 77% and 30% of men, respectively [67]. In females, 57% developed ovarian failure [67] and is overall more common in females who are post-pubertal at the time of HSCT [28]. Females who are pre-pubertal at transplantation may require hormone therapy to develop secondary sexual characteristics, yet there are reports of spontaneous puberty [27–28, 75]. Discussions about the risks of gonadal dysfunction and infertility should be individualized, and pre-HSCT sperm and ovarian cryopreservation should be offered [76] with the knowledge that some methods are only available on research protocols and often are paid out of pocket. In both myeloablative and non-myeloablative conditioning regimens, rarely patients have conceived children naturally and have delivered healthy babies after HSCT [7, 27, 38], in contrast to promising data in patients with thalassemia [77–79]. As has been shown in patients with thalassemia, fertility may be better preserved when HSCT is performed in young, prepubertal children, where the risk of gonadal damage may be attenuated by reduced toxicity regimens, though when not possible, hormonal therapy may be of benefit [77–80].

7. Gene therapy for sickle cell disease

Genetic modification or correction of a patient's autologous HSCs eliminates two major barriers in the cure of SCD: the lack of suitable donors, and the morbidity and mortality

associated with GVHD. After decades of ongoing research, gene therapy for the cure of SCD is now a reality and is being investigated in multiple clinical trials (Table 5).

The field of gene therapy has evolved tremendously over the last 3 decades, becoming safer, more efficient, and available for patients with a variety of disorders. The concept that gene therapy may ameliorate human genetic diseases emerged in the 1970s, with proof of principle and clinical successes emerging throughout the 1990s and early 2000s initially in primary immunodeficiency disorders [81–86]. More than 300 gene therapy trials were registered with the NIH by 2000, however the first trials in hemoglobinopathies, and SCD in particular, were not opened until the latter part of the 2000s in part due to the challenges associated specifically with β -globin expressing vectors, and the need for regulated, lineage specific, high level globin expression. Results from the aforementioned allogeneic HSCT studies demonstrate the need for sustained mixed chimerism to overcome the pathologic, shortened lifespan of sickle cell RBCs, with a requirement of at least 20% donor myeloid chimerism to reverse the sickle phenotype [87]. The identification and characterization of the β -globin locus control region (LCR), a powerful erythroid-specific enhancer required for high level globin gene expression, along with its hypersensitivity sites, was critical for the success of gene therapy in hemoglobinopathies given early retroviral studies without the LCR elements showed <1% β globin expression [88].

Early mouse models demonstrated the first successful amelioration of β -thalassemia with transgene expression of nearly 20% of the total hemoglobin using a human β -globin lentiviral vector with LCR fragments (TNS9 and β A vectors), demonstrating that the hematologic and pathologic improvement depended on a vector copy number (VCN) of at least 3 in each HSC [89–91]. Similar lentiviral constructs in SCD mouse models resolved anemia, reduced organ damage, and expressed up to 20–25% vector hemoglobin with 2.2–3 vector copies per HSC utilizing a mutant β -globin gene where glutamine is substituted for threonine at amino acid 87 (β T87Q, LentiGlobin BB305) + two additional γ -globin based substitutions (β AS3) conferring anti-sickling properties [92–93].

Potential methods for gene therapy in SCD are multiple: addition of β -globin to make adult hemoglobin (HbA), addition of γ -globin to increase fetal hemoglobin (HbF) expression, editing of globin regulatory elements, knockdown of HbF repressors to increase HbF expression, or direct gene editing of the sickle mutation with targeted nucleases such as zinc-finger nucleases (ZFNs), transcription-activator like effector nucleases (TALENs), meganucleases, and the clustered, regularly interspaced palindromic repeats (CRISPR) associated nuclease Cas9. Initial trials in gene addition evaluating patients with transfusion dependent β -thalassemia treated with β T87Q (HGB-204, NCT01745120) demonstrated transfusion independence for nearly all individuals with non-Hb β 0 β 0 thalassemia (HbE β 0, Hb β 0 β +, β + β +thalassemia) and a 63% reduction in transfusion requirements for Hb β 0 β 0-thalassemia patients with a vector derived increase in hemoglobin of 3.6–9.6 g/dL and a total hemoglobin of 9.3–13.7 g/dL [94–96]. A similar study, HGB-205 (NCT02151526), included and reported on the first gene therapy patient in SCD, a 13-year-old male with HbSS, reporting a total hemoglobin level of 12.4 g/dL 30 months post-gene therapy, with 6.1 g/dL (49%) of the patient's hemoglobin attributable to β T87Q [97–98]. The patient had no clinical symptoms or complications of SCD until, at about 30 months post-treatment,

the patient developed pain following an episode of acute gastroenteritis with fever and dehydration and was subsequently hospitalized. Two more patients with SCD have been treated on this protocol, with 6 and 3 months of follow-up. At approximately 6 months post-treatment, one of these patients experienced an episode of ACS and was hospitalized. Despite this hospitalization, neither patient has undergone transfusions since Day 21 and 15 post-infusion, with a total Hb of 8.8 g/dL and 9.8 g/dL and HbAT87Q of 1.8 and 1.5 g/dL, respectively, as of last follow-up [98]. No adverse events related to LentiGlobin BB305 have been reported to date.

A similar trial, HGB-206, was opened in the US as an open-label Phase 1 study designed to evaluate the safety and efficacy of LentiGlobin BB305 product in up to 29 adults with severe SCD (NCT02140554). As of July 21, 2017, 9 patients with severe SCD (median age 26 [range 18–42] years) have received LentiGlobin drug product (DP)[99]. Initial reports show no safety concerns related to the DP but lower gene transfer efficiency. In 2016, the HGB-206 protocol was modified to increase DP vector copy number (VCN), require pre-harvest transfusions, increase target busulfan levels, and explore the use of plerixafor for mobilization and apheresis for cell collection. The initial 7 patients (group A) had a median cell dose of 2.1×10^6 CD34+ cells/kg, median DP VCN of 0.6 copies/diploid genome, 8%–42% CD34+ cells transduced, median VCN in peripheral blood of 0.1 (0.1–0.2) copies/genome, and a median HbAT87Q level of 0.9 g/dL (0.4–2.4 g/dL) at median follow-up of 18mo. The 2 newly treated patients (group B, with increased DP VCN and pre-harvest transfusions) had cell doses of 2.2 and 3.2×10^6 CD34+ cells/kg, improved DP VCNs of 1.4/3.3 and 2.9/5.0 (2 DP lots per patient) corresponding to peripheral blood VCN of 2.6 and 0.5 at month 1 and month 3, respectively, and improvement in total percent of CD34+ cells transduced (46%–95%). An additional 8 patients have been enrolled in HGB-206 as of July 21, 2017 but have not yet received DP. For both HGB-205 and HGB-206 thus far, patient CD34+ HSCs were collected via BM harvest, though there may be advantages to utilizing Plerixafor mobilized PBSCs [100–104]. An open trial is investigating the escalation of Plerixafor for mobilization of CD34+ HSCs and evaluating globin gene transfer in patients with SCD (NCT02193191)[105]. In the first three patients reported, there is an impressive improvement in total cell dose of 15.3, 5.6, and 9.0×10^6 CD34+ cells/kg in contrast to BM harvest collection which has yielded a mean of 5.0 (range 0.3–10.8) $\times 10^6$ CD34+ cells/kg per harvest (N=21). Furthermore, ex vivo cultured CD34+ cells isolated from plerixafor mobilized peripheral blood contained an average of 8.2% (1.5–19.5%) CD34dim cells in contrast to an average of 41.0% (17.3%–50.7%) CD34dim cells isolated from BM harvest. In unpublished results characterizing SCD BM compared to healthy volunteers without SCD, we have found SCD BM is characterized by increased inflammation, aggregation, and contamination within the mononuclear layer contributing to significant differences in HSC quality and yield [106]. CD34+ HSCs in SCD BM are characterized by a majority (>50%) CD34dim population and lineage restricted progenitors likely incapable of long-term engraftment that worsen with delays in processing, further supporting the use of Plerixafor mobilization over BM as a source of HSCs. Given the potential advantages of mobilized PBSCs, HGB-206 has included a Plerixafor mobilized arm into its trial design. Other gene addition trials (NCT02247843, NCT02186418) and fetal

hemoglobin trials (NCT03282656) are ongoing, with promising CRISPR/Cas9 gene editing strategies currently in preclinical work [107].

8. Coverage and cost considerations

The Affordable Care Act (ACA) was passed by Congress, then signed into law by President Barack Obama on March 23, 2010 aiming to address the rising costs of healthcare and provide insurance for the tens of millions of Americans who were uninsured [108]. While much of it has been challenged politically, the inability to deny patients with SCD and other pre-existing conditions coverage has remained one of the most popular aspects of this legislation. Additional benefits for patients with SCD include the ability to obtain affordable expert medical care, the expansion of state Medicaid coverage, coverage for preventive services such as pneumonia and influenza vaccinations at no cost share, and expanded coverage under the Dependent Coverage Provision (DCP) where 18–25 year old SCD patients are able to remain on their parent's insurance until the age of 26. The DCP has allowed these patients to access private insurance at a greater rate with increased use of less costly outpatient care [109], critically important given the rise in mortality rates during the transition period from pediatric to adult medical care [110].

Continued access to affordable health insurance is essential in a chronic disease with cumulative organ damage. SCD management becomes costlier over time with total lifetime charges to an individual living to age 50 exceeding \$8 million, rising from patient fees of \$200,000 ages 0–5 to over \$7 million for patients 17–50 years of age [111]. SCD in the US accounts for an estimated \$1.6 billion per year in healthcare costs [112] and ranks fifth among the top ten diagnoses of hospital stays among Medicaid super-utilizers [113]. Whereas maximizing HU therapy, optimizing management of sickle cell pain, and discovering new therapeutic targets is essential, a greater focus on curative approaches for this disease is needed and may be the best available approach to reduce personal lifetime healthcare costs while simultaneously improving quality of life. Whereas the upfront costs of HSCT and gene therapy are high, quality-adjusted life-years (QALYs) gained and the potential to reduce overall lifetime healthcare costs may render curative therapy cost-effective. Median HSCT cost per patient is estimated at \$467,747 (range: \$344,029–\$799,219) [114], though this may be nearly 50% lower in patients who receive a non-myeloablative regimen [115]. Costs for gene therapy are less certain and rumored to be as high as \$500,000–\$1.5 million on social media, however companies have not given estimates and many aspects will go into the cost model, including a need to shift from fee-for-service to value-based payment systems [116].

There are significant issues around how to finance immediate costs for benefits that may occur much later, and more research is needed to evaluate the economic and QALY impacts of curative therapies for the treatment of severe SCD. Current data suggest healthcare utilization post-HSCT is significantly reduced [7, 114] and quality of life is improved [43, 72, 117], though a recent registry study from Belgium reported a survival advantage for patients treated with HU compared to those who underwent HSCT. Follow-up is limited for this study and includes a large proportion of patients with HbSC and HbSβ+ thalassemia who have milder disease courses and would not likely be candidates for HSCT [118]. A

previous hypothetical model suggested HSCT does not have a significant QALY advantage over CT for patients with an elevated cerebral blood flow velocity, however outcomes for HSCT have improved since this study, and highlights the need for non-hypothetical research [119]. Hidden costs are often not factored into healthcare estimates, including loss of wages due to frequent healthcare visits and unemployment among patients and parents. Furthermore, there is no dedicated data on improvement in mental health conditions such as depression after curative therapy that similarly affects healthcare expenditures. Mental health conditions such as depression are 5 times higher in patients with SCD, and total health care costs for adult SCD patients with depression are more than double those of SCD patients without depression [120]. Improved quality of life may mitigate depression in some, and less healthcare utilization may translate into improved job stability and sustained access to health care coverage. Such improvements directly benefit patients and their families, and potentially reduce overall healthcare expenditures.

The substantial healthcare utilization and cost of SCD-related morbidity suggests that a greater focus on curative approaches for this disease is needed. SCD, and particularly severe SCD, is a chronic disease with numerous costly complications and uncertainties that worsen throughout a patient's life. More research is needed to accurately assess the economic implications of curative therapies and more time is needed to avoid underestimating the positive impacts of a high upfront cost intervention. A curative option that seeks to alter the deleterious effects and course of a chronic disease must be viewed in the long term and within an insurance model that ultimately values outcome.

9. Conclusion

SCD can be cured with allogeneic HSCT and autologous HSCT utilizing gene therapy, with the former being underutilized due to a lack of suitable donors and concerns over long term effects of HSCT, and the latter only recently starting in clinical trials. While risks must be weighed against the benefits of any medical intervention, the ability to cure patients, a lack of overt SCD manifestations post allogeneic HSCT, and stabilization or improvement of subclinical SCD pathology, reinforces the notion that conventional BMT offers a favorable risk-benefit balance for those patients with severe SCD who are living with a devastating, life limiting disease with limited therapeutic options to reduce disease severity. Where there are limitations in donor availability, conditioning regimens, graft rejection, or life threatening GVHD, studies into non-myeloablative conditioning regimens, expanded donor sources, and improved post-HSCT supportive care are promising. And after many years of preclinical work and advances in gene therapy for hemoglobinopathies, several clinical trials for SCD gene therapy are ongoing and show an additional hopeful promise for a cure for patients with SCD.

10. Expert Commentary

SCD is a curable disease. Whereas newborn screening, penicillin prophylaxis, and vaccinations have significantly reduced early childhood mortality, the only two currently available treatments for SCD, blood transfusions and HU, are not free of side effects, and do not fully eliminate the consequences of the disease. HSCT offers patients a chance for cure

but is limited by donor availability, patient referral when an HLA-matched sibling donor is available, and lack of clear evidence for success outside of the HLA-matched sibling donor setting including unrelated donor BM and UCBT, and haploidentical HSCT. Despite these current limitations, there is a concerted effort in the scientific community to have a better understanding of SCD pathophysiology, to develop and trial targeted drug therapies, to refine transplantation methods and expand the donor pool, and to bring gene therapy models to fruition. Given the scarcity of available treatments for SCD, each of these contributions are significant, and aim to reduce disease burden, improve outcomes and quality of life for patients with SCD, and ultimately will reduce health care costs over the long term.

To enable other HSCT methods to become standard of care, improvements in conditioning regimens, improved and refined donor/recipient HLA-matching, identification of anti-HLA antibodies, and improved effectiveness of GVHD prophylaxis are needed. Whereas HSCT may not be economically and practically feasible in developing countries, focus on new drug development is imperative, and includes understanding γ -globin expression, inhibiting polymerization and developing anti-sickling strategies, understanding the rheological properties of RBCs, and targeting the inflammatory cascade known to characterize much of the pathophysiology of SCD. Advancements in drug development and transplantation methods, including gene therapy, are limited, however, by cost, and overall patient willingness to enroll on clinical trials given a well-founded historical mistrust of the medical community. Despite this, our experience tells us that the sickle cell community sees incredible promise in the current SCD field and feel great hope for both the short and long-term goals to treat and cure this devastating disease. Advocates, providers, and researchers see the tools to create significant impacts in the treatment of SCD. Most importantly, patients and their family members feel that their deserved hopes for medications to reduce disease burden, and for more widely available curative options, will soon be realized.

11. Five-year view

SCD is the most common inherited hemoglobinopathy worldwide and is a devastating, life-limiting disease in many with few currently available therapeutic options. In 2018, there are two FDA approved therapies, and despite starting with only a 10–15% chance of having an HLA-identical donor, only 10% of eligible patients have undergone curative HSCT despite patient willingness to consider HSCT morbidity and mortality at the chance for cure. Whereas current medical therapies for SCD are limited, the interest and expansion of scientific research is thriving. Dozens of new drugs are being investigated, transplantation methods are being expanded and refined, and after decades of research, the promise of gene therapy for the cure of SCD is now a reality with multiple open clinical trials and preliminary evidence showing its success. Within the next 5 years, we surmise there will be numerous new open clinical trials in addition to FDA approved oral and IV therapies aimed at reducing VOCs, reducing inflammation and cell adhesion, and modifying hemoglobin to reduce RBC sickling. HSCT methods, in particular haploidentical transplantation and immune therapy conditioning, will be more widely available. In 2023, the first gene therapy patients will be nearly 10 years out from transplantation, with success from the most recently transplanted patients with the refined processing method realized. Important improvements in drug manufacturing, transduction efficiency, transplantation conditioning,

and patient optimization prior to transplantation will allow gene addition strategies to move into phase 3 clinical trials, with expansion shortly thereafter into the pediatric population. Gene editing strategies with CRISPR technology have more unanswered questions, but will likely move away from mouse models, toward primate models, and eventually into clinical trials as further understanding of HSCs and DNA repair are uncovered. Clinical trials for gene editing will likely focus first on editing the genes regulating fetal hemoglobin expression before trials aim to directly correct the sickle mutation, primarily as the former does not require homology directed repair. Lastly, legislative awareness and funding for SCD research, surveillance, prevention, and treatment is likely to enhance our knowledge and our ability to advance the science. Both the US House of Representatives (H.R. 2410) and the US Senate (S.2465) have proposed SCD legislation, appropriating \$4.5 million for each of fiscal years 2018 through 2022. As there has been no explicit governmental funding for SCD since 2009, the marriage of legislative support and funding with the scientific rigor will likely result in tremendous advancements over the next five years in the treatment and cure of SCD.

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12.

Key Issues

- Sickle cell disease is the most common inherited hemoglobinopathy worldwide, and is a devastating, life limiting disease with limited therapeutic options to reduce disease severity.
- Hematopoietic stem cell transplant with either bone marrow, umbilical cord blood, or peripheral blood stem cells should be considered the standard of care for patients with symptomatic SCD and an HLA-matched sibling donor given and overall and event free survival of >90%.
- Stable mixed chimerism with a reduction rather than an elimination of hemoglobin S is sufficient to overcome the pathogenic phenotype. Non-myeloablative but immunosuppressive conditioning regimens reduce toxicity and therefore may afford more patients the ability to undergo hematopoietic stem cell transplant who would otherwise be limited by myeloablative conditioning. A large review of myeloablative vs. non-myeloablative conditioning in over 1000 patients show no difference in overall and event free survival based on the preparative regimen.
- When there is not an HLA-identical sibling, alternative donor sources should be pursued for symptomatic patients with SCD and done only on a clinical trial. Results for unrelated bone marrow and cord blood transplantation are conflicting, with high rates of graft rejection, graft-vs-host disease (GVHD), and treatment related mortality. Better conditioning regimens, improved and refined donor/recipient HLA-matching, higher cell dose for cord blood, identification of anti-HLA antibodies, and improved effectiveness of GVHD prophylaxis are needed.
- Haploidentical transplantation promises an expanded donor pool of biological parents, biological children, full or half siblings, or even extended family donors to patients with SCD who otherwise satisfy eligibility requirements for HSCT but lack a suitable matched related or unrelated donor. Goals for haploidentical protocols include lowering treatment related mortality and improving engraftment while lowering the risk of GVHD by employing in vivo and ex vivo T cell depletion methods.
- Gene therapy for hemoglobinopathies has been limited by challenges associated specifically with β -globin expressing vectors, and the need for regulated, lineage specific, high level globin expression. Many advances in gene therapy techniques and strategies have been made over the last several decades, now allowing the promise of gene therapy for the cure of sickle cell disease to become a reality as it now being tested in multiple clinical trials.

Table 1. Myeloablative Hematopoietic Stem Cell Transplantation for Sickle Cell Disease Patients with HLA-identical sibling donors

Study	Walters, 1996/2000/2001 (6, 8, 32)	Vernylen, 1998 (30)	Bernaudin, 2007 (28)	Pane Pinto, 2007 (31)	Lucarelli, 2014 (25)	Bhatia, 2014 (26)	McPherson, 2011 (29)	Dedeken, 2014 (27)
Location	USA (multicenter)	Belgium	France	CIBMTR	Rome	USA (NY)	USA (Atlanta)	Belgium
Dates	1991–2000	1986–1997	1988–2004	1989–2002	2004–2013	NR	1993–2007	1988–2013
Number	59	50	87	67	40	18	27	50
Age range (yrs)	3–15	9mo–23	2–22	2–27	2–17	2–20	3–17	1–15
Source(BM/CB)	59/0	48/2	74 **/10	54/4	40/0	15/3	27/0	39/3
Preparative Regimen	BU 14mg/kg, CY 200mg/kg, ATG/ Alemtuzumab	BU 16mg/kg, CY 200mg/kg +/- TLI or ATG	BU 16mg/kg, CY 200mg/kg +/- ATG	BU 16mg/kg, CY 200mg/kg	BU 14mg/kg, CY 200mg/kg, ATG, +/- Flu	BU 13–16mg/kg, Flu 180mg/m ² , Alemtuzumab	BU 14mg/kg, CY 200mg/kg, ATG	BU 13–18mg/kg, CY 200mg/kg +/- ATG +/- HU
GVHD prophylaxis	CsA +/- MTX +/- pred	CsA +/- MTX	CsA +/- MTX	CsA, MTX	CsA, MTX, pred	Tacrolimus, MMF	CsA, MTX	CsA, MTX
OS	93%	93%	93%	97%	91%	100%	96%	94%
EFS	84%	82%	86%	85%	91%	100%	96%	86%
Rejection	8%	10%	7%	13%	0	0	0	8%
TRM	7% (n=4)	2% (n=1)	7% (n=6)	4% (n=3)	9% (n=3)	0	4% (n=1)	4%
GVHD * (acute/ chronic)	19% (acute + chronic)	20%/20%	20%/13%	10%/22%	18%/5%	17%/11%	12%/4%	22%/20%
% Donor Chimerism	11–100%; 26% stable mixed chimerism	<10%–100%	5–95%; 25–40% with mixed chimerism	9 had mixed red cell chimerism (Hb S >50%)	25–100%	86–93%	62–100%	15–100%
Complications	Seizures 48%; GVHD was the main cause of TRM (n=3)	Seizures 36%	Seizures 16%; GVHD was the main cause of TRM (n=4)	Seizures 20%	Seizures 23%; GVHD was the main cause of TRM (n=3)		Seizures 16%; GVHD was the main cause of TRM (n=1)	Seizures 22%
End Organ Changes	No post-transplant pain, stroke or ACS after engraftment; Those with a prior history of stroke had stable or improved cerebral imaging	Recovery of spleen function present in 7/10; Gonadal dysfunction present in those (6 boys, 8 girls) transplanted around puberty	No new ischemic lesions were detected after engraftment, and cerebral velocities were significantly reduced		No post-transplant pain, stroke or ACS	Neurological, pulmonary and cardiovascular function were stable or improved at 2 years		All patients with elevated arterial cerebral velocities before HSCT had conditional or normal values afterwards
Notes	In response to neurologic complications, anticonvulsant therapy was added, and parameters were set for BP, Hb, Plt count, and Mg level	Group of 14 asymptomatic patients (median age 2y) transplanted before returning to Africa had lower rejection and GVHD	Rejection rate dropped from 22.6% to 3%, and EFS increased to 95% when ATG was added; CB transplant recipients did not develop GVHD; No TRM after the 40 th transplant or with CB	Approximately half of those who rejected received more than 10 blood transfusions prior to HSCT	No deaths in non-Black African patients	Reduced toxicity conditioning regimen. All episodes of GVHD resolved	Lower busulfan AUC was seen with partial donor chimerism versus full donor chimerism (P=0.022)	EFS at 8y (97.4%) was significantly higher than EFS in those who did not receive HU prior to HSCT (58.3%) (p<0.001)

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ACS: acute chest syndrome, ATG: Anti-thymocyte globulin, AUC: area under the curve, BM: Bone marrow, BP: blood pressure, BU: busulfan, CB: cord blood, CIBMTR: Center for International Blood and Marrow Transplant Research, CsA: Cyclosporine, CY: Cyclophosphamide, EFS: event free survival, Flt: fludarabine, GVHD: graft versus host disease, Hb: hemoglobin, HSCT: hematopoietic stem cell transplantation, HU: hydroxyurea, ICH: intracranial hemorrhage, Mg: magnesium, MTX: Methotrexate, NR: not reported, Plt: platelet, Pred: Prednisone, OS: overall survival, TLI: total lymphoid irradiation, TRM: treatment related mortality.

* GVHD grade II-IV.

** 4 patients had 1 HLA antigen mismatch

Table 2.

Non-Myeloablative Hematopoietic Stem Cell Transplantation for Sickle Cell Disease Patients

Study	Horan, 2005 (35)	Iannone, 2003 (36)	Jacobsohn, 2004 (37)	Hsieh, 2009 (38)	Krishnamurti, 2008 (44)	Shenoy, 2005 (45)	Hsieh, 2014 (7)	Matthes-Martin, 2013 (46)	Saraf, 2016 (43)
Location	USA (Rochester)	USA (multicenter)	USA (Chicago)	USA (NIH)	USA (multicenter)	USA (St. Louis)	USA (NIH)	Austria	USA (Chicago)
Dates	2001–2002	1999–2001	2000–2004	NR	NR	2001–2004	2004–2013	2004–2011	2011–2014
Number	3	6	3	10	7	1	30	8	13
Age range (years)	9–30	3–20	4–22	16–45	6–18	2	16–65	3–24	17–40
Source(BM/CB)	3/0	6/0	0/0^	0/0^	7/0	1/0	0/0^	7/1	0/0^
Preparative Regimen	Flu 125 mg/m2, ATG, 200 cGy TBI	Flu 150 mg/m2, 200 cGy TBI +/- ATG	BU 6.4 mg/kg, Flu 180 mg/m2, ATG	300 cGy TBI, Alemtuzumab	BU 6.4mg/kg IV or 8mg/kg PO, Flu 175mg/kg, ATG, 500 cGy TLI	Flu 150 mg/m2, Melphalan 140 mg/m2, Alemtuzumab	300 cGy TBI, Alemtuzumab	Flu, Melphalan +/- Thiotepa or TBI + ATG or Alemtuzumab	300 cGy TBI, Alemtuzumab
GVHD prophylaxis	MMF, CsA	MMF, CsA or tacrolimus	CsA, MMF	Sirolimus	CsA, MMF	CsA +/- MMF +/- methyIpred	Sirolimus	CsA, MMF	Sirolimus
OS	100%	100%	67%	100%	100%	100%	97%	100%	100%
EFS	33%	0	0	90%	86%	100%	87%	100%	93%
Rejection	67%(n=2)	100%(n=6)	67% (n=2)	10%(n=1)	14%(n=1)	0	13%(n=4)	0	7%(n=1)
TRM	0	0	33% (n=1)	0	0	0	0	0	0
GVHD * (acute/ chronic)	0/0	17%/0	0/100%	0/0	7%/7%	0/0	0/0	0/0	0/0
% Donor Chimerism	0–100%(n=1)	25–85% while on immune suppression	9–100%	7–72% lymphoid; 19–100% myeloid	50–90%	>95%	34–62% lymphoid; 70–100% myeloid	20–97%; 8/8 have 100% donor erythropoiesis	Median 81% (31–98%)
Complications/ End Organ Changes/ Notes	Pure red cell aplasia in engrafted patient due to major ABO incompatibility; One patient had a stroke during period of low engraftment; In patient with stable chimerism, no sickle-related complications have occurred, and pulmonary function has improved. Rejection occurred in all but one after immune suppression was weaned	During the period of mixed chimerism, none experienced pain, ACS, or stroke; All patients rejected their grafts once immune suppression was weaned	Death due to extensive chronic GVHD	Weaned 4 patients off narcotics post-transplantation	All patients had stable head imaging and lung function as measured by pulmonary function testing. Normal renal function was regained in all patients; 5 patients had splenic regeneration	**Risk factors for rejection included multiple transfusions (6), low stem cell numbers (1), and immunologic/ metabolic disorders	Serious adverse events (n=38) were related to pain, infection, abdominal events, and sirolimus related toxic effects, however no acute sickle cell-related complications, hepatic sinusoidal obstructive syndrome, or cerebral complications from immunosuppression; Fifteen engrafted patients discontinued immunosuppression with stable donor chimerism and no GVHD	Renal volume and structure normalized in 4/5 patients with nephropathy; All patients showed normal growth; 3/4 female postpubertal patients had regular gonadal hormone levels	Patient with secondary graft failure was not compliant with sirolimus; Patients had normalized hemoglobin concentrations and improved cardiopulmonary and QoL parameters including bodily pain, general health, and vitality

ACS: acute chest syndrome, ATG: Anti-thymocyte globulin, BM: Bone marrow, BU: busulfan, CB: cord blood, CsA: Cyclosporine, CY: Cyclophosphamide, EFS: event free survival, Flu: fludarabine, GVHD: graft versus host disease, MMF: mycophenolate mofetil, MTX: Methotrexate, NR: not reported, Pred: Prednisone, OS: overall survival, TBI: total body irradiation, TRM: treatment related mortality.

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*GVHD grade II-IV.
^All donor sources were GCSF CD34+ mobilized peripheral blood stem cells.
**Includes 15 patients with other non-malignant diseases.

Table 3.

Alternative Donor Sources for Hematopoietic Stem Cell Transplantation in Sickle Cell Disease Patients

	Umbilical Cord Blood						Unrelated Bone Marrow	
Study	Locatelli, 2003 (53)	Adamkiewicz, 2007 (54)	Radhakrishnan, 2013 (55)	Ruggeri, 2011 (56)	Kamani, 2012 (57)	Locatelli, 2013 (50)	Shenoy, 2016 (58)	Krishnamurti, 2015 (59)
Location	Eurocord	USA (multicenter)	USA (New York)	Retrospective review	USA (multicenter SCURT trial)	Eurocord, Oakland	USA (multicenter SCURT trial)	USA (multicenter STRIDE trial)
Dates	1994–2001	NR	2004–2010	1996–2009	2008–2012	1994–2005	2008–2014	2012–2015
Number	11	7	8	16	8	160	29	22
Age range (years)	1–12	1–12	1–10	3–17	7–16	1–24	6–19	17–36
Source(BM/CB)	CB	CB	CB	CB	CB	130/30	29/0	22/0
Relationship	Related	Unrelated	Unrelated	Unrelated	Unrelated	Related	Unrelated	17 Related/5 Unrelated
HLA Match	6/6 (n=41); 5/6 (n=3)**	5/6 (n=2); 4/6 (n=5)	NR	6/6 (n=2); 5/6 (n=4); 4/6 (n=10)	5/6 (n=8)	HLA-identical	8/8 (n=29)	8/8 (n=22)
Total Nucleated Cell Dose (range)	4.0 × 10 ⁷ /kg (1.2–10)**	5.7 × 10 ⁷ /kg (1.5–9.3)	NR	4.9 × 10 ⁷ /kg (1.1–9)	6.4 × 10 ⁷ /kg (3.1–7.6)	3.9 × 10 ⁷ /kg(NR)	3.5 × 10 ⁸ /kg (1.3 – 6.8)	NR
Median CD34+ Cell Dose (range)	NR	2.3 × 10 ⁵ /kg (0.5–6)	NR	NR	1.5 × 10 ⁵ /kg (0.2–2.3)	NR	2.9 × 10 ⁶ /kg (0.3–9.2)	NR
Preparative Regimen	BU, CY, ATG/ Alemtuzumab +/-TT, Flu	BU 3.5mg/kg-40mg/m ² , CY 50–60mg/kg, Flu 25–35mg/m ² , ATG +/- TLI 200–750 cGy	BU 3.2–4mg/kg, Flu 30mg/m ² , Alemtuzumab	Combinations of BU, CY, ATG, Flu, melphalan, Alemtuzumab, TLI/TBI	Flu 30mg/m ² , Melphalan 140mg/m ² , Alemtuzumab	BU 16mg/kg, CY 200mg/kg +/- Treosulfan +/- Flu +/-ATG	Flu 30mg/m ² , Melhalan 140mg/m ² , Alemtuzumab	Bu 13.2 mg/kg, Flu 150mg/m ² , ATG
GVHD prophylaxis	CsA +/- MTX +/- tacrolimus +/- pred	CsA, methypred +/- MMF +/- tacro	MMF, Tacro	CsA or Tacro or Pred or MMF or MTX	CsA or Tacrolimus + MMF	CSA +/- MTX	CsA or Tacrolimus, MTX, methylpred	CsA or Tacrolimus, MTX
OS	100%	43%	63%	94%	88%	95%/97% ⁺	79%	95%
EFS	90%	43%***	50%	50%	38%	92%/90% ⁺⁺	69%	95%
Rejection	9%	43%	38%	44%	63%	7%/10% ⁺	10%	0
TRM	0	14% (n=1)	38% (n=3)	6% (n=1)	13% (n=1)	5% (n=18)/3% (n=3) ⁺	28% (n=8)	5% (n=1)
GVHD [*] (acute/ chronic)	11%/6%**	57%/14%	50%/13%	23%/16% [^]	25%/13%	21%/11% (acute) ⁺ 12%/7% (chronic)	28%/62%	0/14%
% Donor Chimerism	45–100%	75–76%	NR	9 with complete donor chimerism	3 with complete donor chimerism	NR	>90%	87.5% T cell and 100% myeloid

Umbilical Cord Blood							Unrelated Bone Marrow	
Study	Locatelli, 2003 (53)	Adamkiewicz, 2007 (54)	Radhakrishnan, 2013 (55)	Ruggeri, 2011 (56)	Kamani, 2012 (57)	Locatelli, 2013 (50)	Shenoy, 2016 (58)	Krishnamurti, 2015 (59)
Complications/ Notes	Use of MTX for GVHD prophylaxis was associated with a greater risk of treatment failure	57% (n=4) developed significant viral infections	Three deaths were due to infection in patients with primary graft failure	1 death from chronic GVHD; In multivariate analysis, DFS was higher with CB units containing total nucleated cell dose >5 × 107/kg	19 infections in 6 patients; 2 serious neurologic complications (ICH, PRES); 1 death from chronic GVHD; Cord blood arm of this trial was therefore suspended due to high incidence of graft rejection	GVHD was the most frequent cause of death in patients after BM transplantation, whereas no CB recipient died of GVHD. Cell dose did not influence outcomes.	GVHD was the main cause of TRM (n=7). A 34% incidence of PRES noted; Although the 1-year EFS met the target (75%), this regimen is not sufficiently safe for widespread use without modifications for more effective GVHD prophylaxis	6 severe adverse events in 4 patients including one death from ICH related to PRES

ATG: Anti-thymocyte globulin. BM: Bone marrow. BU: busulfan, CB: cord blood, CsA: Cyclosporine, CY: Cyclophosphamide, EFS: event free survival, Flu: fludarabine, GVHD: graft versus host disease, ICH: intracranial hemorrhage, MMF: mycophenolate mofetil, MTX: Methotrexate, NR: not reported, Pred: Prednisone, PRES: posterior reversible encephalopathy syndrome, OS: overall survival, TLI: total lymphoid irradiation, TRM: treatment related mortality, TT: Thiotepa.

* GVHD grade II-IV.

** Includes 33 patients with thalassemia and 11 patients with SCD in the cohort; HLA typing specifically for SCD not reported.

*** Patient rejected graft eight months after first failed UCBT but developed sustained engraftment after a second UCBT with an immunosuppressive but not myeloablative regimen.

^ Includes 35 patients with thalassemia and 16 patients with SCD in the cohort.

+ Includes 325 patients with thalassemia and 160 patients with SCD in the cohort. Percentages for the entire cohort bone marrow/umbilical cord blood.

+/- Disease free survival for sickle cell cohort only, bone marrow/umbilical cord blood.

Table 4.

Haploidentical Transplantation for Sickle Cell Disease Patients

	Haploidentical Bone Marrow Transplantation	
Study	Bolaños-Meade, 2012 (62)	Dallas, 2013 (64)
Location	USA (Johns Hopkins)	USA (St. Jude)
Dates	2006–2011	NR
Number	14	8
Age range (years)	15–42	4–17
Relationship	Related	Related
HLA Match	NR	3/6 (n=6); 4/6 (n=2)
Total Nucleated Cell Count	4.35 × 108/kg (4.6–5.2)	450 × 106 cells/kg (10–1890)
Median CD34+ Cell Dose (range)	5.24 × 106/kg (4.4–8.7)	25.4 × 106/kg (6–57)
Median CD3+ cell count (range)	3.61 × 107/kg (3.29–6.59)	0.07 × 106/kg (0.006–0.168)
Preparative Regimen	Flu 30mg/m2, CY 14.5 mg/kg, TBI 200 cGy, ATG	Flu 150–200 mg/m2, Thiotepa, BU, ATG, muromonab-CD3 or HU, Azathioprine, BU, Thiotepa, CY, muromonab-CD3
GVHD prophylaxis	CY 50mg/kg, Tacrolimus or Sirolimus, MMF	MMF
OS	100%	75%
EFS	50%	38%
Rejection	50%	38%
TRM	0	25% (n=2)
GVHD * (acute/chronic)	0/0	40%/75%
% Donor Chimerism	11–100%	100%
Complications	GVHD was the main cause of TRM (n=2)	
End Organ Changes	<p><i>PRES was not encountered in the patients who received sirolimus instead of tacrolimus (incidence 21% for patients on tacrolimus)</i></p> <p><i>No clinical evidence of new cerebrovascular events, ACS, or priapism has been recorded on engrafting patients</i></p>	<p><i>There was no stroke, pulmonary hypertension, ACS, proteinuria, or hematuria observed in patients after successful HSCT; however, the patients who underwent myeloablative MRD HSCT demonstrated progressive declines in renal, pulmonary, and cardiac function over time that have not been reported previously**</i></p>
Notes	<p><i>Pain medicines were eventually tapered in 10 of the 11</i></p> <p><i>Of the 2 patients who died, one had received the highest CD3+ dose in the graft, and the other developed severe chronic lung GVHD after receiving a DLI</i></p>	

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Haploidentical Bone Marrow Transplantation		
	Bolaños-Meade, 2012 (62)	Dallas, 2013 (64)
Study	<i>patients with evidence of engraftment; Rejection rate reported at 43% however an additional patient had 5% chimerism and return of SCD</i>	

ACS: acute chest syndrome, ATG: Anti-thymocyte globulin, BU: busulfan, CY: Cyclophosphamide, DL: donor lymphocyte infusion, EFS: event free survival, Flu: fludarabine, GVHD: graft versus host disease, HSCT: hematopoietic stem cell transplantation, MMF: mycophenolate mofetil, MTX: Methotrexate, NR: not reported, PRES: posterior reversible encephalopathy syndrome, OS: overall survival, TBI: total body irradiation, TRM: treatment related mortality.

* GVHD grade II-IV.

** Study also reported on 14 patients who underwent matched related donor hematopoietic stem cell transplantation.

Table 5.

Active and Open Trials for Hematopoietic Stem Cell Transplant in Sickle Cell Disease

ClinicalTrials.gov Identifier	Title	Status	Regimen	Donor Source	Age	N	Start Date	Study Objective	Location
NCT03279094	Haploidentical Transplantation With Pre-Transplant Immunosuppressive Therapy for Patients With SCD	Recruiting	Myeloablative	Haploidentical	1–30	15	October 2017	To evaluate safety and toxicity of 2 cycles of pre-transplant immunosuppressive therapy followed by myeloablative preparative regimen and allogeneic HSCT from a haploidentical donor	USA, California City of Hope Medical Center
NCT02678143	A Pilot Study of Nonmyeloablative Conditioning for Mismatched HSCT for Severe SCD	Recruiting	Non-myeloablative	Haploidentical, Mismatched unrelated	> 19	20	April 26, 2016	To evaluate safety and feasibility of non-myeloablative conditioning in haploidentical or one antigen mismatch unrelated HSCT for adult patients with severe SCD	USA, Missouri Washington University
NCT02867800	Abatacept for GVHD Prophylaxis After HSCT for Pediatric SCD	Recruiting	Reduced Intensity	Unrelated	3–20	10	July 2016	To assess tolerability of the costimulation blocking agent abatacept (CTLA4-Ig) when added to standard GVHD prophylaxis	USA and Canada, multicenter
NCT03298399	MSCs for Haploidentical HSCT for SCD	Recruiting	NR	Haploidentical	12–40	18	September 1, 2017	To determine safety, tolerability, and effects on engraftment and GVHD of autologous, BM derived MSCs in patients with SCD undergoing haploidentical HSCT	USA, Georgia Children's Healthcare of Atlanta, Emory
NCT03214354	Nonmyeloablative SCT in Children With SCD and a Major ABO-Incompatible Matched Sibling Donor (Sickle-MAID)	Recruiting	Non-myeloablative	Matched related	1–19	12	July 5, 2017	To evaluate safety and efficacy of nonmyeloablative conditioning for allogeneic HSCT in pediatric patients with SCD who have a matched related major ABO-incompatible donor	Canada, Alberta Alberta Children's Hospital
NCT01499888	Ph I/II Study of Allogeneic SCT for Clinically Aggressive SCD	Recruiting	Non-myeloablative	Matched related	16–60	15	November 11, 2011	To determine engraftment and transplant related morbidity and mortality after non-myeloablative allogeneic HSCT using immune-suppressive agents and low-dose TBI without standard chemotherapy in patients with aggressive SCD	USA, Illinois University of Illinois at Chicago
NCT02435901	HSCT For Patients with High Risk Hemoglobinopathies Using Reduced Intensity	Recruiting	Reduced Intensity	Related or unrelated BM, matched or mismatched BM	1–21	19	December 2008	To evaluate use of RIC regimen in patients with high risk hemoglobinopathy SCD and B-Thalassemia Major in combination with standard immunosuppressive medications, followed by a routine SCT	USA, New York Cohen Children's Medical Center of New York
NCT03121001	Study of HLA-SCT to Treat Clinically Aggressive SCD	Recruiting	Reduced Intensity	Haploidentical	16–60	50	April 28, 2017	To determine engraftment at Day +60 following HLA-haploidentical HSCT protocol using immunosuppressive agents and low-dose TBI for conditioning and post-transplant cyclophosphamide	USA, Illinois University of Illinois at Chicago
NCT02165007	Haploidentical HSCT	Recruiting	Reduced Intensity	Haploidentical, CD34+ selected graft	Up to age 22	15	January 2015	To assess safety and toxicity of RIC haploidentical HSCT using CD34+ selected graft	USA, D.C. Children's National Medical Center
NCT02105766	Nonmyeloablative PB Mobilized HPCT for SCD and Beta-thalassemia in People with Higher Risk of Transplant Failure	Recruiting	Non-myeloablative	HLA-matched	16–80	162	April 1, 2014	To see if low dose radiation (300 rads), oral cyclophosphamide, pentostatin, and sirolimus help a body to better accept donor stem cells	USA, Maryland National Institutes of Health
NCT02038478	Allograft for SCD and Thalassemia	Recruiting	Non-myeloablative	HLA-matched	18–45	50	January 2014	To determine safety and therapeutic potential of a nonmyeloablative PB Mobilized HPCT	USA, Texas UT Southwestern Medical Center

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ClinicalTrials.gov Identifier	Title	Status	Regimen	Donor Source	Age	N	Start Date	Study Objective	Location
NCT03077542	Nonmyeloablative Haploidentical PB Mobilized HPCT for SCD	Recruiting	Non-myeloablative	Haploidentical	2–80	84	April 6, 2017	To evaluate safety, efficacy, and tolerance of a nonmyeloablative Haploidentical PB Mobilized HPCT for SCD	USA, Maryland National Institutes of Health
NCT02766465	BMT vs Standard of Care in Patients with Severe SCD (BMT CTN 1503) (STRIDE2)	Recruiting	Myeloablative	HLA-matched related or unrelated donor	15–40	200	November 2016	To compare BMT to standard care	USA, multicenter
NCT01917708	BMT Abatacept for Non-Malignant Diseases	Recruiting	Reduced Intensity	Unrelated adult donor (marrow or PBSC) or an unrelated CB unit	Up to age 21	20	January 2014	To assess the tolerability of abatacept when combined with CsA and MMF as GVHD prophylaxis	USA, Georgia Children’s Healthcare of Atlanta
NCT02757885	Transplantation Using Reduced Intensity Approach for Patients with SCD Disease From Mismatched Family Donors of Bone Marrow (TRANSFORM)	Recruiting	Reduced Intensity	Mismatched family donor BM	15–40	15	April 2016	To learn if it is possible and safe to treat persons with severe SCD by HSCT from human leukocyte antigen (HLA) half-matched related donors	USA, Georgia Children’s Healthcare of Atlanta
NCT00061568	Improving the Results of Bone Marrow Transplantation for Patients with Severe Congenital Anemias	Recruiting	Non-myeloablative	HLA-matched	2–80	150	May 23, 2003	Evaluate nonmyeloablative conditioning in adults with severe SCD	USA, Maryland National Institutes of Health
NCT01962415	RIC for Non-Malignant Disorders Undergoing UCBT, BMT or PBSCT (HSCT+RIC)	Recruiting	Reduced Intensity	4/6, 5/6 or 6/6 HLA matched related or unrelated UCB or 8/8 or 7/8 HLA matched unrelated donor BM or PB progenitor graft	2mo-35	30	February 4, 2014	To evaluate efficacy of using a RIC regimen with UCBT, double cord UCBT, matched unrelated donor, BM transplant or PBSC transplant in patients with non-malignant disorders	USA, Pennsylvania Children’s Hospital of Pittsburgh of UPMC
NCT01850108	Non-Myeloablative Conditioning and BMT	Recruiting	Non-myeloablative	HLA-matched related donor or Haploidentical	2–70	25	May 2013	To evaluate efficacy of a non-myeloablative regimen for partially HLA-mismatched and HLA-matched BM	USA, Tennessee Vanderbilt-Ingram Cancer Center
NCT01049854	CD34+Selection for Partially Matched Family or Matched Unrelated Adult Donor HSCT	Recruiting	Myeloablative Arm and Reduced Intensity Arm	NR	Up to age 70	35	September 2011	To evaluate efficacy of CD34+ selection for patients with a partially matched or matched unrelated donor	USA, New York New York Medical College
NCT03249831	Non-Myeloablative Conditioning Regimen with Haploidentical T-Cell-Depleted PB Transplant for Patients with Severe SCD	Not yet recruiting	Non-myeloablative	Haploidentical	18–45	6	November 2017	To evaluate safety and feasibility of non-myeloablative conditioning and CD4+ T cell depleted grafts for haploidentical HSCT	USA, California City of Hope Medical Center
NCT00745420	Evaluating the Safety and Effectiveness of BMT in Children with SCD (BMT CTN 0601)	Active, not recruiting	Reduced Intensity	Unrelated BM	3–19	39	August 2008	To evaluate the safety and effectiveness of using BM from unrelated donors in children with severe SCD who receive RIC	USA, multicenter
NCT00977691	Nonmyeloablative Haploidentical PB Mobilized HPCT for Severe Congenital Anemias Including SCD and Beta-Thalassemia	Active, not recruiting	Non-myeloablative	Haploidentical	>2	59	September 9, 2009	To determine if a haploidentical BMT, low-intensity radiation, immunosuppressant drugs, and no chemotherapy will be effective in patients with SCD and Beta-thalassemia. To determine the effectiveness of cyclophosphamide in preventing rejection of the donor cells	USA, Maryland National Institutes of Health
Gene Therapy Trials									
NCT02140554	A Study Evaluating the Safety and Efficacy of the LentiGlobin BB305 Drug Product in Severe SCD	Recruiting	NR	Gene Therapy	> 18	29	August 2014	To evaluate gene therapy by transplantation of autologous CD34+ stem cells transduced ex vivo with the LentiGlobin BB305 lentiviral vector in subjects with severe SCD	USA, multicenter

ClinicalTrials.gov Identifier	Title	Status	Regimen	Donor Source	Age	N	Start Date	Study Objective	Location
NCT03282656	Gene Transfer for SCD	Recruiting	NR	Gene Therapy	3–35	7	November 30, 2017	To evaluate feasibility of HSC gene transfer for SCD using autologous BM derived CD34+ HSCs transduced with a lentiviral vector containing a short-hairpin RNA targeting BCL11a	USA, Massachusetts Boston Children’s Hospital
NCT02186418	Gene Transfer for Patients With SCD	Recruiting	NR	Gene Therapy	18	10	July 2014	To determine whether transfer of a fetal hemoglobin gene using a Gamma Globin Lentivirus Vector into human blood making cells is safe and feasible in patients with SCD	USA and Jamaica, Cincinnati Children’s Hospital Medical Center
NCT02247843	Stem Cell Gene Therapy for Sickle Cell Disease	Recruiting	Cytoreductive	Gene Therapy	>18	6	July 2014	Assess the safety and initial evidence for efficacy of an autologous transplant of pAS3-FB vector transduced BM CD34+ cells for adults with severe SCD	USA, California University of California, Los Angeles
NCT02151526	A Study Evaluating the Efficacy and Safety of LentiGlobin BB305 Drug Product in Beta-Thalassemia Major and SCD	Active, not recruiting	NR	Gene Therapy	5–35	7	July 2013	To evaluate safety and efficacy of the administration of LentiGlobin BB305 Drug Product to subjects with either beta-thalassemia major or severe SCD	Paris, France

BM: bone marrow, BMT: bone marrow transplant, CsA: cyclosporine, HPCT: hematopoietic precursor cell transplantation, HSCT: hematopoietic stem cell transplantation, MMF: mycophenolate mofetil, PB: peripheral blood, PBSC: peripheral blood stem cells, MSC: mesenchymal stromal cells, NR: not reported, RIC: reduced intensity conditioning, SCD: sickle cell disease, TBI: total body irradiation, UCBT: umbilical cord blood transplant