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Review

Curative therapy for hemoglobinopathies: an International Society for Cell & Gene Therapy Stem Cell Engineering Committee review comparing outcomes, accessibility and cost of *ex vivo* stem cell gene therapy versus allogeneic hematopoietic stem cell transplantation

Alexis Leonard[1], Alice Bertaina[2], Carmem Bonfim[3], Sandra Cohen[4], Susan Prockop[5], Duncan Purtill[6], Athena Russell[7], Jaap Jan Boelens[8,9], Robert Wynn[10], Annalisa Ruggeri[11,*], Allistair Abraham[12,*,**]

[1] *Division of Hematology, Children's National Hospital, Washington, DC, USA*
[2] *Division of Hematology, Oncology, Stem Cell Transplantation and Regenerative Medicine, Department of Pediatrics, Stanford University, Stanford, California, USA*
[3] *Pediatric Bone Marrow Transplantation Division, Hospital Pequeno Principe, Curitiba, Brazil*
[4] *Université de Montréal and Maisonneuve Rosemont Hospital, Montréal, Canada*
[5] *Stem Cell Transplantation and Cellular Therapies, Department of Pediatrics, Memorial Sloan Kettering Cancer Center, New York, New York, USA*
[6] *Department of Haematology, Fiona Stanley Hospital, Perth, Australia*
[7] *Center for Cellular Immunotherapies, University of Pennsylvania, Philadelphia, Pennsylvania, USA*
[8] *Stem Cell Transplantation and Cellular Therapies, Memorial Sloan Kettering Cancer Center, New York, New York, USA*
[9] *Department of Pediatrics, Weill Cornell Medical College of Cornell University, New York, New York, USA*
[10] *Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, UK*
[11] *Department of Hematology and bone marrow transplantation, IRCCS Ospedale San Raffaele, Segrate, Milan, Italy*
[12] *Center for Cancer and Immunology Research, CETI, Children's National Hospital, Washington, DC, USA*

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ABSTRACT

Thalassemia and sickle cell disease (SCD) are the most common monogenic diseases in the world and represent a growing global health burden. Management is limited by a paucity of disease-modifying therapies; however, allogeneic hematopoietic stem cell transplantation (HSCT) and autologous HSCT after genetic modification offer patients a curative option. Allogeneic HSCT is limited by donor selection, morbidity and mortality from transplant conditioning, graft-versus-host disease and graft rejection, whereas significant concerns regarding long-term safety, efficacy and cost limit the broad applicability of gene therapy. Here the authors review current outcomes in allogeneic and autologous HSCT for transfusion-dependent thalassemia and SCD and provide our perspective on issues surrounding accessibility and costs as barriers to offering curative therapy to patients with hereditary hemoglobinopathies.

Introduction

Thalassemia major and sickle cell disease (SCD) are the two most frequent hereditary hemoglobinopathies in the world. The annual birth rate is estimated to increase from the current 300 000 to over 400 000 births in the next several decades, 80% of which occur in low- or middle-income countries [1]. Thalassemia major and SCD therefore represent a growing global health burden, and treatment options that aim to reduce the burden of disease are needed.

Despite a significant increase in survival for patients with thalassemia with regular blood transfusions, iron chelation therapy, evidence-based practice guidelines, splenectomy and antibiotic prophylaxis [2,3], complications directly from transfusion therapy or indirectly from iron overload and organ damage increase the medical burden of disease as much as 10–15% per patient [4–6]. Recently, luspatercept (previously called ACE-536) was approved by the Food and Drug Administration for the treatment of adults >18 years of age with transfusion-dependent thalassemia (TDT) as an agent that improves red blood cell (RBC) maturation by an incompletely understood mechanism.

Hydroxyurea (HU) is efficacious in reducing SCD-related complications and is therefore a routine consideration as early as 9 months of age before protective fetal hemoglobin (HbF) levels fall and SCD-

** Correspondence: Allistair Abraham, MD, Center for Cancer and Immunology Research, Cell Enhancement and Technologies for Immunotherapy, Children's National Hospital, 111 Michigan Avenue NW, Washington, DC 20010, USA.
E-mail address: aabraham@childrensnational.org (A. Abraham).
* These authors contributed equally to this work.

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related complications begin to occur [7–10]. HU must, however, be continued indefinitely with close monitoring, which may contribute to low uptake and adherence. Newer Food and Drug Administration-approved therapies include L-glutamine and crizanlizumab to reduce pain events and voxelotor to improve anemia; however, the role of these drugs in the management of patients with SCD remains unclear. In addition, the costs of these new drugs provide additional barriers to broad access. Similarly, chronic blood transfusion therapy requires a patient's time and commitment, carries the risk of iron overload and alloimmunization and does not fully eliminate the complications of the disease.

Given the burden of disease and limitations of disease-modifying therapies currently available for SCD and TDT, curative strategies are needed. As RBC disorders, both SCD and TDT can be cured by hematopoietic stem cell transplantation (HSCT); however, the use of HSCT is limited in both conditions by a paucity of available HLA-identical sibling donors and well-matched unrelated donors (MUDs) [11,12]. Although allogeneic HSCT is limited by donor availability, morbidity and mortality from transplant conditioning, graft-versus-host disease (GVHD) and graft rejection, gene therapy, either by gene addition or gene modification, targeting autologous hematopoietic stem cells (HSCs) may become a universal cure for SCD and TDT that eliminates the major limitations of allogeneic transplantation. Here the authors review and provide perspectives on the outcomes, accessibility and cost of *ex vivo* stem cell gene therapy versus allogeneic HSCT in TDT and SCD.

Indications for and Limitations of Allogeneic HSCT for TDT and SCD in the Current Era

Transfusion dependence due to thalassemia is the principal indication for HSCT. Challenges of providing blood, chelation therapy, adequate monitoring and patient support, particularly in developing countries, hinder transfusion with chelation as an effective treatment modality [13]. Children with TDT and a suitable, unaffected, HLA-identical sibling should be offered HSCT as early as possible to avoid complications associated with chronic transfusions and iron overload. Outcomes from HSCT correlate with severity of iron overload and duration of exposure; thus, outcomes are best in individuals in whom the risks of organ damage from excess iron stores have been minimized [14].

Clinical phenotypes of SCD are extremely variable, and there is no clear definition of symptomatic SCD; thus, unlike TDT, there are no universal, widely adopted indications for HSCT in SCD. The presence of central nervous system disease is generally acceptable for HSCT given the risk of second overt strokes or progressive cerebral infarcts despite adequate transfusion therapy [15,16]. Recurrent vaso-occlusive crisis (VOC) despite HU, recurrent acute chest syndrome, osteonecrosis, sickle nephropathy, red cell alloimmunization, pulmonary hypertension and recurrent splenic sequestration encompass other "severe" disease complications that may be considered indications for HSCT [17], but most of these reflect expert opinion.

HSCT for either TDT or SCD is limited by disease complications, the preparative regimen and the graft source, all of which contribute to peritransplant morbidity and mortality. Patients with both TDT and SCD exhibit ineffective erythropoiesis; therefore, mixed donor chimerism is sufficient in part because of the competitive advantage of donor RBCs [18–20]. Studies investigating reduced intensity conditioning (RIC) regimens have reported similar overall survival (OS) and event-free survival (EFS) with lower toxicity [21–23] compared with myeloablative regimens. However, standard preparative regimens currently utilize myeloablation to efficiently lower the barrier for engraftment and minimize graft rejection, and therefore some patients are excluded from HSCT based solely on the ability to tolerate myeloablation. Some modifications may be made in high-risk patients [24–28]; however, deviation from myeloablative therapy remains under investigation and is currently done under clinical trials. Furthermore, both TDT and SCD patients exhibit an intact immune system, and hyperinflammation specific to SCD, requiring sufficient immunosuppression for sustained engraftment. In general, patients with stable donor engraftment after HSCT do not experience sickle-related complications after HSCT in SCD, or require ongoing transfusion support in TDT, with stabilization or even improvement in end-organ pathology. However, this is balanced by a significant risk of infertility, which remains a major barrier and important concern for patients and families [22,23,29–32].

Outcomes: Allogeneic HSCT in TDT and SCD

HLA-matched sibling donor HSCT

The effectiveness of HSCT for TDT with HLA-matched sibling donor was established in the 1980s [33], with reported OS and disease-free survival (DFS) now approaching 91% and 83%, respectively, with bone marrow (BM) from HLA-identical siblings [34]. Similarly, proof of concept for cure of SCD after HSCT occurred in 1984 when a child with sickle cell anemia developed acute myelogenous leukemia (AML) and was cured of both her AML and SCD after HLA-matched sibling HSCT [35]. Since then, over 1000 patients with SCD have successfully undergone HSCT with an HLA-identical sibling donor, with greater than 90% of all patients cured of SCD [36,37]. Table 1 is a partial summary of HLA-identical HSCT in TDT and SCD over the last 5 years.

Initial experiences in matched sibling HSCT in TDT formalized three independent prognostic factors (Pesaro classification): hepatomegaly >2 cm, portal fibrosis and history of inadequate iron chelation therapy [38]. DFS of 87%, 85% and 80% for Pesaro class I, II and III recipients, respectively, demonstrated that optimal lifelong transfusion and chelation therapy, preventing anemia and iron-related tissue damage, is critical for transplant success. Subsequently, age >14 years was established as an independent risk factor [39], though after adjusting for donor type and conditioning regimen, new data suggest the best outcome is in patients aged ≤6 years [40]. Modifications in conditioning with the addition of Thiotepa (TT) have improved outcomes for patients with Pesaro class III recipients [41].

Similarly, the largest international survey of results of HLA-identical sibling HSCT in SCD identified several key factors associated with survival after transplantation: age, graft type and transplant period [36]. The 5-year EFS and OS of over 1000 patients worldwide were 91.4% and 92.9%, respectively; there was no difference in EFS or OS based on preparative regimen (myeloablative versus non-myeloablative); EFS decreased with increasing age at transplantation; and EFS improved in patients transplanted after 2006 given improvements in supportive care and prevention and management of complications. The use of non-myeloablative or RIC regimens is more common in SCD than TDT, currently demonstrates an acceptable OS and EFS with very little morbidity or GVHD [22,23,42–46] and is being trialed in patients with TDT [47]. By using reduced toxicity with immunomodulatory conditioning, engraftment is still achieved and allows older adults who have accumulated end-organ damage, those refractory to HU, and those who have developed severe alloimmunization to be eligible for curative therapy.

Compared with BM as the source of HSCs, HLA-matched sibling cord blood (CB) is associated with similar OS and DFS but decreased rates of both acute GVHD (aGVHD) and chronic GVHD (cGVHD) in patients with hemoglobinopathies [48]. Conversely, compared with BM, significantly higher rates of both aGVHD and cGVHD are reported when peripheral blood stem cells (PBSCs) are used in patients with TDT, despite similar 2-year OS and DFS [49]. In SCD, lower OS is demonstrated for PBSC transplanation recipients compared to those receiving BM as a stem cell source [36].

Table 1
Allogeneic Transplant for TDT and SCD

Author (reference)	Published	Disease	Number	Myeloablation	OS	EFS	aGVHD/cGVHD
Matched Sibling Donors							
Saraf (44)	2016	SCD	13	No	100%	93%	0/0
Baronciani (39)	2016	TDT	1061	NR	91%	83%	7%/5%
Gaziev (41)	2016	TDT[+]	37	Yes	92%	92%	28%/6%
Gluckman (36)	2017	SCD	1000	Yes (n=873; 87%)	92.9%	91.4%	14.8%/14.3%
Eapen (37)	2019	SCD	558	Yes (n=348; 62%)	96.2%	90.7%	11.6%/18.1%
Li (40)	2019	TDT	677	Yes	89%	86%	11.8%/8.3%
Guilcher (43)	2019	SCD	16	No	100%	100%	0/0
Krishnamurti (45)	2019	SCD	22[*]	No	94%	94%	18%/29%
Bernaudin (117)	2020	SCD	234[**]	Yes	97%	93.9%	20.1%/10.5%
Shin (47)	2020	TDT, SCD	9(TDT);4(SCD)	No	91.7%	91.7%	20%/20%
Swaminathan (53)	2020	TDT	177	Yes	95%	96%	41%/17%
Alzahrani (46)	2021	SCD	122	No	93%	87%	1.6%/0
Matched Unrelated/Mismatched Cord Blood Donors							
Shenoy (57)	2016	SCD	29	No	79%	69%	28%/62%
Abraham (18)	2017	SCD	9	No	100%	78%	33%/33%
Li (40)	2019	TDT	252	Yes	87%	82%	21.5%/8.4%
Sun (56)	2019	TDT	48	Yes	100%	100%	8.3%/8.3%
Gluckman (59)	2020	SCD	71	Yes	88%	62%	23%/23%
Gluckman (58)	2020	SCD	144^	Yes	86%	72%	24%/24%
Swaminathan (53)	2020	TDT	58	Yes	87%	84%	60%/20%
Feng (68)	2021	TDT	10	Yes	90%	80%	44%/67%
Haploidentical Donors							
Fitzhugh (73)	2017	TDT, SCD	2(TDT);21(SCD)	No	87%	50%	0/0
Gilman (83)	2017	SCD	8	No	88%	88%	25%/13%
Gaziev (82)	2018	TDT, SCD	11(TDT);3(SCD)	Yes	84%	69%	28%/21%
Pawlowska (75)	2018	SCD	4	Yes	100%	100%	0/75%
de la Fuente (77)	2019	SCD	15	No	100%	93%	20%/6%
Foell (81)	2019	SCD	20	No	90%	90%	35%/30%
Bolanos-Meade (72)	2019	TDT, SCD	5(TDT);12(SCD)	No	100%	94%	24%/18%
Cairo (78)	2019	SCD	19	Yes	84%	84%	6.2%/6.7%
Foell (85)	2020	SCD	25	Yes	88%	88%	28%/16%
Anurathapan (79)	2020	TDT	83	Yes	96%	96%	42%/45%

aGVHD: acute graft-vs-host-disease; cGVHD: chronic graft-vs-host-disease; NR: not reported; SCD: sickle cell disease; TDT: transfusion dependent thalassemia. [+] TDT class 3 recipients treated with a modified preparatory conditioning regimen.
[*] Entire cohort (n=22) included 17 patients who received marrow from an HLA-identical sibling donor and 5 patients who received marrow from an 8/8 HLA-allele matched unrelated donor.
[**] French series of 234 patients with SCD who received a matched-sibling-donor stem cell transplantation following standardized myeloablative conditioning between 1988 to 2012. ^Cohort (n=144) includes data on 70 unrelated adult donors (49%), six unrelated cord blood (4%), and 68 haploidentical donors

The authors agree with recommendations from the European Society for Blood and Marrow Transplantation working groups suggesting that young TDT patients with an available HLA-identical sibling should be offered HSCT as soon as possible before development of iron overload and iron-related tissue damage [1], transplant-related risk factors should be evaluated according to the Pesaro risk score [2], CB and BM from HLA-matched sibling donors are equally effective stem cell sources [3] and routine use of PBSC transplantation should be avoided because of the increased risk of cGVHD [4]. With regard to patients with SCD, young patients with symptomatic SCD who have an HLA-matched sibling donor should be transplanted as early as possible, preferably at pre-school age, with unmanipulated BM or CB [34].

Alternative donor outcomes

Despite some improvements in alternative donor outcomes, HSCT from a non-HLA-matched sibling donor should be considered an experimental approach and should be conducted in the context of well-designed trials. Table 1 is a partial summary of unrelated donor and haploidentical HSCT in TDT and SCD over the last 5 years.

Unrelated donors

MUD HSCT in TDT is limited by a high incidence of aGVHD and cGVHD and inferior OS and DFS compared with matched sibling HSCT [50–53]. A higher risk of alloreactive reactions is noted with higher Pesaro risk class and older age, and improved results are reported with high-resolution molecular typing for both HLA class I and II molecules and according to stringent criteria of compatibility with the recipient [54,55]. In an attempt to improve outcomes, changes to preparative regimens have been trialed [24,56]. TT and fludarabine were added to the classic preparative busulfan (Bu)/cyclophosphamide (Cy)-based regimen, reducing the Bu dose by one third to decrease lung and liver toxicity [24]. No statistically significant difference was observed between the matched sibling and MUD groups in terms of 3-year OS, treatment-free survival, treatment-related mortality, cumulative incidence of graft failure and grade III–IV aGVHD. Expert recommendations are if a well-MUD is available, allogeneic HSCT is a suitable option for a child with lifelong control of iron overload and absence of iron-related tissue complications. The unrelated donor must be selected using high-resolution molecular typing for both HLA class I and II loci and according to stringent criteria of compatibility with the recipient [34] and BM as stem cell source.

The current experience with MUD HSCT for SCD is limited, with mixed results, and primarily restricted by high rates of GVHD and rejection [57–59]. A reduced-toxicity regimen is now being tested in a comparative trial of HSCT and standard of care based on the availability of a suitable HLA-matched related or unrelated donor (BMT CTN 1503, NCT01565616).

Unrelated umbilical CB HSCT is reported to have high rates of graft failure and delayed hematopoietic recovery secondary to low stem cell content [60,61]. In SCD, trials using unrelated CB are limited by

small numbers and show high rates of graft rejection and infection [48,61–65]. The umbilical CB arm of the sickle cell unrelated donor transplant trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0601) was suspended because of a high incidence of graft rejection and low DFS [63]. The conditioning regimen has been modified to include HU and TT, with a reported DFS and OS in nine patients of 78% and 100%, respectively, with 33% GVHD (n = 3) at a median follow-up of 2 years [18]. When higher cell doses were used in TDT, the 5-year OS and EFS were 88.3% and 73.9%, respectively [66]. Strategies to improve outcomes in unrelated CB HSCT include the use of multiple CB units [67,68]; combining CB with T-cell-depleted, HLA-haploidentical CD34+ HSCs [69]; and *ex vivo* expansion of umbilical CB-derived stem and progenitor cells [70,71].

Haploidentical donors

The major challenge of HLA-haploidentical HSCT is bidirectional alloreactivity leading to a high incidence of graft rejection and GVHD. T-cell depletion strategies (i.e., *in vivo* post-transplant Cy [PTCy] or *ex vivo* CD34+ selection of donor grafts) reduce recipient T cells that recognize the disparate HLA of the haploidentical donor cells and cause graft rejection while also reducing donor T-cell-mediated GVHD. HLA-haploidentical transplantation with PTCy in patients with SCD and TDT demonstrates high OS, limited toxicity and effective reduction of aGVHD and cGVHD in most studies [72–78]. Increasing total body irradiation to 400 cGy resulted in 100% OS and 94% EFS (SCD, n = 12, β-thalassemia, n = 5), resolution of all GVHD at last follow-up and independence from transfusion in five patients with TDT [72]. The increase in total body irradiation to 400 cGy and addition of TT to the preparative regimen appear to improve engraftment and are being assessed in an ongoing multi-center trial for SCD (BMT CTN 1507, NCT03263559). In TDT, pre-transplant pharmacologic immunosuppression followed by a reduced-toxicity conditioning regimen resulted in a 3-year OS and EFS of >96% each, and 7% severe GVHD in a cohort of 83 patients [79]. Reports of *ex vivo*$\alpha\beta$ T-cell receptor/CD19+-depleted grafts or CD3+-depleted/CD34+-selected grafts are limited by small numbers of patients, investigating various conditioning and GVHD prophylactic regimens and reported generally lower EFS and OS and higher GVHD than the PTCy protocols [80–85]. Infectious complications from delayed immune reconstitution and associated morbidity and mortality remain problematic with this overall strategy. Despite these overall improvements in haploidentical models, patient numbers remain small, and more study data are therefore needed to guide clinical practice.

Outcomes: Gene Therapy in TDT and SCD

Gene transfer outcomes in TDT

A broad strategy in genetic modification for thalassemia includes insertion of a functional globin gene that sufficiently corrects the globin chain imbalance that is characteristic of thalassemia. This strategy offers wide applicability, given that there are more than 200 individual thalassemia mutations identified, and can be done using lentiviral (LV) transduction of a normally functioning β-globin gene into autologous HSCs that are then infused as autologous HSCT after myeloablative conditioning. Clinical trials investigating gene transfer for TDT are listed in Table 2.

NCT01745120 and NCT02151526 reported data on 22 patients with TDT who underwent autologous HSCT after transduction with an anti-sickling variant of β-globin (β^{T87Q}, LentiGlobin BB305) [86]. At a median follow-up of 26 months (range, 15–42), all but one of the 13 patients who had a non-$\beta0/\beta0$ genotype stopped receiving red cell transfusions, and nine patients with a $\beta0/\beta0$ genotype or two copies of the IVS1-110 mutation had a median annualized transfusion volume reduction of 73%, with discontinuation of RBC transfusions in three (33%) patients. Levels of HbA^{T87Q} ranged from 3.4 g/dL to 10.0 g/dL (total hemoglobin [Hb], 8.2–13.7 g/dL). Treatment-related adverse events were typical of those associated with myeloablative Bu. No clonal dominance related to vector integration was observed. This protocol is now being investigated in two phase 3 studies for patients with TDT (NCT03207009) and patients with TDT who do not have a $\beta0/\beta0$ genotype (NCT02906202). Based on the phase 1/2 results, the European Medicines Agency approved this LV product, which contains approximately 24–400 million autologous CD34+ cells transduced with HbA^{T87Q}, in 2019 for individuals 12 years and older who have TDT with a non-$\beta0/\beta0$ genotype.

NCT02453477 reported data on nine subjects with TDT after direct intra-bone injection of HSCs transduced with the GLOBE LV vector, which encodes a β-globin gene with a modified enhancer region [87]. With a median follow-up of 18 months, transfusion requirement was eliminated in three of the four evaluable children and was reduced in three adults. Younger age and persistence of higher vector copy number in the repopulating HSCs were associated with better outcome. Adverse events were chemotherapy-related; there were no vector-related concerns. NCT01639690 is investigating transduction with TNS9.3.55, an LV vector encoding the normal β-globin gene; however, data have not yet been reported.

Gene transfer outcomes in SCD

Gene addition strategies in SCD involve the addition of an anti-sickling β-globin or γ-globin cassette that overcomes the impaired erythropoiesis associated with sickle Hb. Clinical trials investigating gene transfer for SCD are listed in Table 2. In general, participants undergo a period of transfusions prior to PBSC mobilization and apheresis with plerixafor followed by myeloablative conditioning and cell infusion. Protocols initially used BM harvest as a source of autologous HSCs; however, recent reports suggest higher CD34+ cells/kg yield after plerixafor mobilization, improved transduction efficiency and improved HSC quality compared with BM from subjects with SCD [88–93].

The largest current experience in gene therapy for SCD is the phase 1/2 study evaluating the safety and efficacy of autologous CD34+ HSCs transduced with β^{T87Q}, LentiGlobin BB305 (NCT02140554) [94–97]. This has evolved over three cohorts, and as of March 3, 2020, 40 Group C patients (age, 12–38 years) have initiated cell collection and 25 have been treated with the drug product (DP), with a follow-up period of 2.8–24.8 months [95]. In the 16 evaluable patients with ≥6 months of follow-up, total Hb has ranged from 9.6 g/dL to 16.2 g/dL, with an HbA^{T87Q} contribution of 2.7–9.4 g/dL and median HbS ≤60% of total Hb. There is near pancellular expression of HbA^{T87Q} ≥6 months post-treatment, with approximately 90% of RBCs containing βA^{T87Q} by 18 months and reduction in sickling propensity comparable to sickle cell trait. At last visit post-treatment, key hemolysis markers were trending toward normalization, and no patients required RBC transfusions. Post-treatment, no acute chest syndrome or serious VOCs were observed, and participants reported clinically meaningful improvements in pain reduction at 12 months post-treatment (n = 5).

On February 16, 2021, NCT02140554 and NCT04293185 were placed on a temporary suspension because of a reported suspected unexpected serious adverse reaction (SUSAR) of AML [98]. A patient from the initial Group A of NCT02140554 developed AML 5 years after gene therapy, and the trial was halted to determine if there was any relationship to the use of the LV vector. Additionally, a second SUSAR of myelodysplastic syndrome in a patient from Group C of NCT02140554 is currently being investigated. Prior to suspension, there was one death in Group A related to Bu conditioning and unrelated to LV therapy [99], and there was one death in Group C (unlikely related to LentiGlobin) >18 months post-treatment in a patient with significant baseline SCD-related cardiopulmonary disease. Investigations are ongoing to determine the etiology of the

Table 2
Clinical Trials in Gene Transfer for TDT and SCD

Gene Transfer Clinical Trials									
ClinicalTrials.gov Identifier	Start Date	Title	Disease	Status	Phase	Age	N	Study Objective	Location
NCT01639690	2012	ß-Thalassemia Major With Autologous CD34+ Hematopoietic Progenitor Cells Transduced With TNS9.3.55 a Lentiviral Vector Encoding the Normal Human ß-Globin Gene	TDT	Active, not recruiting	1	>18	10	To investigate safety and efficacy of treatment of beta thalassemia major with autologous CD34+ HPCs Transduced With TNS9.3.55 a Lentiviral Vector Encoding the Normal Human ß-Globin Gene	New York, USA
NCT01745120	2013	A Study Evaluating the Safety and Efficacy of the LentiGlobin BB305 Drug Product in β-Thalassemia Major Participants	TDT	Completed	1/2	12-35	19	To evaluate the safety and efficacy of autologous HCT using LentiGlobin BB305 Drug Product [autologous CD34+ hematopoietic stem cells transduced with LentiGlobin BB305 lentiviral vector encoding the human βA-T87Q-globin gene]	USA, multicenter; Sydney, Australia; Bangkok, Thailand
NCT02151526	2013	A Study Evaluating the Efficacy and Safety of LentiGlobin BB305 Drug Product in Beta-Thalassemia Major and SCD	TDT, SCD	Completed	1/2	5-35	7	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
NCT02140554	2014	A Study Evaluating the Safety and Efficacy of the LentiGlobin BB305 Drug Product in Severe SCD	SCD	Suspended	1/2	12-50	50	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
NCT02186418	2014	Gene Transfer for Patients With SCD	SCD	Active, not recruiting	1/2	18-45	10	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, multicenter and Jamaica
NCT02247843	2014	Stem Cell Gene Therapy for SCD	SCD	Active, not recruiting	1/2	>18	6	Assess the safety and initial evidence for efficacy of an autologous transplant of βAS3-FB vector transduced bone marrow CD34+ cells for adults with severe SCD	USA, California
NCT02453477	2015	Gene Therapy for Transfusion Dependent Beta-thalassemia (TIGET-BTHAL)	TDT	Active, not recruiting	1/2	3-64	10	To evaluate safety and efficacy of autologous hematopoietic stem cells genetically modified with GLOBE lentiviral vector encoding for the human beta-globin gene for the treatment of patients affected by TDT	Milano, Italy
NCT02906202	2016	A Study Evaluating the Efficacy and Safety of the LentiGlobin® BB305 Drug Product in Subjects With Transfusion-Dependent β-Thalassemia, Who do Not Have a β0/β0 Genotype	TDT	Active, not recruiting	3	<50	23	To evaluate the efficacy and safety of autologous HCT using LentiGlobin BB305 Drug Product.	USA, multicenter; Marseille, France; Hannover, Germany; Rome, Italy; London, UK
NCT03207009	2017	A Study Evaluating the Efficacy and Safety of the LentiGlobin® BB305 Drug Product in Subjects With Transfusion-Dependent β-Thalassemia	TDT	Active, not recruiting	3	<50	18	To evaluate the efficacy and safety of autologous HCT using LentiGlobin BB305 Drug Product	USA, multicenter; Marseille, France; Germany, multicenter; Thessaloniki, Greece; Rome, Italy; London, UK
NCT03282656	2018	Gene Transfer for SCD	SCD	Suspended	1	3-40	7	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

(*continued on next page*)

Table 2 (*Continued*)

Gene Transfer Clinical Trials									
ClinicalTrials.gov Identifier	Start Date	Title	Disease	Status	Phase	Age	N	Study Objective	Location
NCT04091737	2019	CSL200 Gene Therapy in Adults With Severe SCD	SCD	Active, not recruiting	1	18-45	3	To evaluate the safety of the following: collection of CD34+ HPCs by apheresis after mobilization with plerixafor, reduced intensity conditioning with melphalan, and administration of CSL200 (Autologous Enriched CD34+ Cell Fraction That Contains CD34+ Cells Transduced With Lentiviral Vector Encoding Human γ-GlobinG16D and Short-Hairpin RNA734) in adult subjects with SCD	USA, California
NCT03964792	2019	Safety and Efficacy of Gene Therapy of SCD by Transplantation of an Autologous CD34+ Enriched Cell Fraction That Contains CD34+ Cells Transduced ex Vivo with the GLOBE1 Lentiviral Vector Expressing the βAS3 Globin Gene (DREPAGLOBE)	SCD	Recruiting	1/2	5-35	10	To evaluate the Safety and Efficacy of Gene Therapy of SCD by Transplantation of an Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced ex vivo with the GLOBE1 lentiviral vector expressing the βAS3 globin gene (GLOBE1 βAS3 Modified Autologous CD34+ Cells)	Paris, France
NCT04293185	2020	A Study Evaluating Gene Therapy With BB305 Lentiviral Vector in SCD	SCD	Suspended	3	2-50	35	To evaluate HSC transplantation with Lenti-Globin BB305 Drug Product for SCD	USA, multicenter

HCT: hematopoietic stem cell transplantation, HPC: hematopoietic progenitor cells, SCD: sickle cell disease, TDT: transfusion dependent thalassemia

recent SUSAR events, though an updated report suggests that LV-derived mutagenesis was unlikely [100,101].

The investigators of NCT03282656 recently published data from six participants (age, 7–25 years) who had follow-up for at least 6 months (range, 7–29) after receiving BCH-BB694 gene therapy (LV vector transfer of a short hairpin RNA targeting BCL11a for increased γ-globin expression) [102]. HbF induction at most recent follow-up was 20.4–41.3%, with broad distribution of HbF among red cells. All patients had engraftment, and adverse events were consistent with the effects of preparative chemotherapy. Clinical manifestations of SCD were reduced or absent during the follow-up period. This study has also been paused pending an investigation by the data safety and monitoring board regarding the SUSAR occurrence in the aforementioned, unrelated gene therapy study involving SCD patients.

NCT02186418 is a phase 1/2 study investigating the efficacy and safety of γ-globin gene transfer, and as of July 28, 2020, data from three patients are available [103]. Participants range in age from 19 years to 34 years, with 6–30 months of follow-up. Anti-sickling globin expression ranged from 22% to 38% at last follow-up, there have been no treatment-related adverse events to date and all participants have maintained improvements in vaso-occlusive events.

Gene editing outcomes in TDT

Clinical trials investigating gene editing for TDT are listed in Table 3. Given the several hundred mutations in the β-globin locus that result in TDT, increasing HbF levels rather than directly targeting the β-globin mutation is a strategy for stabilizing the α: non-α globin ratio sufficiently to prevent intra-marrow apoptosis in developing RBCs.

Results from the first TDT patient treated in NCT03655678, a study investigating CRISPR-Cas9 targeting of the BCL11A erythroid-specific enhancer for increased HbF expression, were recently reported [104]. Approximately 80% of the alleles at this locus were modified, with no evidence of off-target editing. More than a year later, there remains high levels of allelic editing in BM and blood and increases in HbF that were distributed pancellularly and had achieved transfusion independence. Levels of HbF increased rapidly, from 0.3 g/dL at baseline to 13.1 g/dL at month 18, with an increase in F-cell expression, from 10.1% at baseline to 99.7% at month 6, maintained through month 18. The patient's Hb level normalized to 12.1 g/dL at month 4 and remained normal through month 18.

Gene editing outcomes in SCD

Clinical trials for gene editing in SCD are focused first on editing HbF expression rather than directly correcting the sickle mutation, as the former does not require homology-directed repair. Clinical trials investigating gene editing for SCD are listed in Table 3.

Preliminary data in the first two participants in NCT03745287, a study investigating CRISPR-Cas9 editing of the BCL11A erythroid-specific enhancer, were recently published [104,105]. Total Hb and HbF% were 10.3 g/dL and 42.4% (12-month follow-up) and 10.0 g/dL and 46.8% (3-month follow-up), respectively. Participants had 7.0 and 7.5 VOCs per year, respectively, prior to enrollment and reported no VOCs after infusion. No other CTX001-related serious adverse events were reported. For one patient with longer follow-up, HbF increased from a baseline of 9.1% to 43.2% at month 15, and F-cell expression was maintained at nearly 100% through month 15 [104]. This participant had no VOC episodes during the 16.6 months after the infusion of gene-modified cells, and the last transfusion of packed red cells was 19 days after infusion.

One additional study, NCT03653247, is evaluating the safety, tolerability and efficacy of autologous HSCT using BIVV003, a gene editing therapy that uses zinc finger nuclease technology. Information

Table 3
Clinical Trials in Gene Editing for TDT and SCD

Gene Editing Clinical Trials									
ClinicalTrials.gov Identifier	Start Date	Title	Disease	Status	Phase	Age	N	Study Objective	Location
NCT03655678, NCT03745287	2018	A Safety and Efficacy Study Evaluating CTX001 in Subjects With Transfusion-Dependent β-Thalassemia (NCT03655678) or Severe SCD (NCT03745287)	TDT, SCD	Recruiting	1/2	12-35	45	To evaluate the safety and efficacy of autologous CRISPR-Cas9 Modified CD34+ Human HPCs using CTX001 (autologous CD34+ HPCs modified with CRISPR-Cas9 at the erythroid lineage-specific enhancer of the BCL11A gene)	USA, multicenter; Canada, multicenter; Rome, Italy; UK, multicenter; Brussels, Belgium
NCT03432364	2018	A Study to Assess the Safety, Tolerability, and Efficacy of ST-400 for Treatment of Transfusion-Dependent Beta-thalassemia (TDT)	TDT	Active, not recruiting	1/2	18-40	6	To understand safety and tolerability of ST-400 (zinc finger nuclease technology to disrupt a the BCL11A enhancer), and secondary objectives are to assess the effects on fetal hemoglobin levels and transfusion requirements	USA, multicenter
NCT04211480	2019	Safety and Efficacy Evaluation of γ-globin Reactivated Autologous Hematopoietic Stem Cells	TDT	Recruiting	NR	5-15	12	To evaluate the safety and efficacy of the treatment with γ-globin reactivated autologous hematopoietic stem cells in subjects with β-thalassemia major using Crispr/Cas9 gene editing system	Shanghai, China
NCT03653247	2019	A Study to Assess the Safety, Tolerability, and Efficacy of BIVV003 for Autologous HCT in Patients With Severe SCD (PRECIZN-1)	SCD	Recruiting	1/2	18-40	8	To evaluate the safety, tolerability, and efficacy of autologous HCT using BIVV003 (zinc finger nuclease messenger ribonucleic acid (mRNAs) targeting the BCL11A locus	USA, multicenter
NCT04443907	2020	Study of Safety and Efficacy of Genome-edited Hematopoietic Stem and Progenitor Cells in SCD	SCD	Recruiting	1/2	2-40	30	To evaluate two genome-edited, autologous, hematopoietic stem and progenitor cell (HSPC) products - OTQ923 and HIX763 - each reducing the biologic activity of BCL11A, increasing fetal hemoglobin (HbF) and reducing complications of SCD	USA, multicenter

HCT: hematopoietic stem cell transplantation, HPC: hematopoietic progenitor cells, SCD: sickle cell disease, TDT: transfusion dependent thalassemia

regarding recruitment and/or preliminary results has not yet been published.

Evidence-Based Assessment of Allogeneic HSCT Versus Gene Therapy in TDT and SCD

Thousands of patients with TDT and SCD have undergone allogeneic HSCT worldwide with high OS [39]. Allogeneic HSCT with either BM or umbilical CB is an established therapeutic option for patients with symptomatic SCD and an HLA-matched sibling donor with an OS and EFS of >90%. Evidence-based assessments for allogeneic HSCT in TDT and SCD are listed in Table 4.

Early gene transfer data demonstrate a possible cure for patients with non-$\beta 0/\beta 0$ TDT and SCD, and may be considered for patients without a matched sibling donor. The decision to pursue an alternative donor source when there is not an HLA-matched sibling versus autologous gene therapy must take into account multiple factors with regard to outcomes, including transplant efficacy, short- and long-term transplant-associated morbidity and mortality, conditioning regimens, patient disease status, donor/patient match, safety, patient preference, donor availability and cost.

The risks associated with genetic manipulation are significant. LV addition strategies require integration into the host genome; therefore, thousands of insertional mutations occur in a population of treated cells. Likewise, off-target CRISPR-induced DNA modifications

Table 4
Evidence Based Assessment for Allogeneic HCT and autologous gene therapy in TDT and SCD

Allogeneic HCT in Thalassemia	
HLA-Matched Sibling	• HLA matched sibling allogeneic HSC represents standard of care for patients with TDT, preferably before the development of iron overload and iron-related tissue damage
Alternative Donors	• If a well-matched unrelated donor is available, allogeneic HSC is a suitable option for a child with life-long control of iron overload and absence of iron-related tissue complications. • The MUD must be selected using high-resolution molecular typing for both HLA class I and II loci, and according to stringent criteria of compatibility with the recipient. • HSC from all other alternative donors should be considered an experimental approach and should be conducted in the context of well-designed clinical trials.
Allogeneic HCT in SCD	
HLA-Matched Sibling	• Matched sibling HSC is a well-established therapeutic option for patients with symptomatic SCD and an HLA-matched sibling donor • There is support for early referral for patients with an HLA-matched sibling
Alternative Donors	• When there is not an HLA-identical sibling, alternative donor sources should primarily be pursued for symptomatic patients with SCD and done on a clinical trial
Gene Therapy in Thalassemia	
Gene Transfer	• Early gene transfer data shows continued requirement of blood transfusions for patients with β0/β0, therefore allogeneic matched sibling HSC is preferred. • When a matched sibling is not available for patients with β0/β0, alternative donor curative HCT vs gene transfer strategies require weighing the individual risks of GVHD and graft failure in alternative donor HCT vs the reduction in transfusion requirement and iron overload with gene transfer-based gene therapy • Gene transfer for non- β0/β0 can be considered as possibly curative, particularly if there is no matched sibling
Gene Editing	• There is insufficient data (patient numbers and length of follow-up) regarding gene editing
Gene Therapy in SCD	
Gene Transfer	• More information regarding the risks of vector derived malignant transformation are required before widespread use of gene addition strategies • If malignant transformation is not related to DP, gene transfer may be considered over alternative donor HSC after weighing risks of GVHD and DFS and potentially malignancy with either option • More data is needed to establish therapeutic benefit of gene transfer vs disease amelioration if production of modified globin is insufficient or wanes over time
Gene Editing	• There is insufficient data (patient numbers and length of follow-up) regarding gene editing

present potentially deleterious off-target effects. Though CRISPR is non-integrating, the requirement for double-stranded DNA breaks may reduce engraftment and proliferative capacity such that a population with proliferative advantages becomes selected for. Though the reports of AML and myelodysplastic syndrome are highly concerning, investigations appear to exonerate vector-mediated dyserythropoiesis [100,101], and multiple factors contribute to the increased risk of post-HSCT malignancy, particularly in patients with SCD [100]. At this time, there are a limited number of patients being treated, and long-term data with regard to gene editing in both TDT and SCD are insufficient to pursue this option without first considering allogeneic HSCT.

Accessibility: Allogeneic HSCT Versus Gene Therapy for Hemoglobinopathies

The evidence-based assessment regarding accessibility of allogeneic HSCT versus gene therapy in hemoglobinopathies takes into consideration location, follow-up needs and patient eligibility and is summarized in Table 5.

Location

Both allogeneic HSCT and gene therapy methods require specialized centers for patient care. Both modalities share a common pretransplant period in which the ability to perform HLA screening and collect stem cells is required. During the peritransplant period, both modalities require prolonged hospitalization and adequate resources to support the patient through conditioning, cell infusion and engraftment. Resources necessary during this period include transfusion support, general laboratory services, pharmacy services, ability to screen for blood-borne infections, ability to escalate care in the event of known potential complications and medical expertise, particularly skilled nursing.

Stem cell collection requires a skilled apheresis team and a stem cell processing laboratory. Gene therapy has the added complexity of cell manufacturing, requiring sophisticated labs that are Good Manufacturing Practice-certified. Additionally, all gene therapy applications are conducted in the setting of a clinical trial and therefore have extensive requirements for screening and monitoring that often include multiple specialties and a large investigative team.

The significant infrastructure and health care provider training required to provide curative options for patients with TDT and SCD have prohibited wide adoption where the burden of disease is greatest. The highest prevalence of disease is found in low- and middle-income countries, where easy access to medical care may be limited. Models for HSCT program development exist and include establishing a global partnership, developing infrastructure and building human resource capacity [106]; however, the long-term sustainability of such programs often depends on government resources, which are often limited. Positive patient outcomes and an economic justification for maintenance of HSCT programs are therefore imperative. At the present time, given the breadth of experience and data in the allogeneic setting, exportability may be more suited to allogeneic HSCT than gene therapy.

Follow-up needs

HSCT conditioning requires myelosuppression to prevent outcompetition by host HSCs and immunosuppression to prevent graft rejection and GVHD. As a result, patients continue to be immunocompromised and require close monitoring and follow-up over a period of months to years. Many variables impact the timing of immune reconstitution, including the conditioning regimen used, source of stem cells and any required manipulation to the graft, degree of HLA match, immunosuppressive therapy, presence of GVHD and use of steroids.

Gene therapy methods have the advantage of not requiring post-HSCT immunosuppression for the prevention of GVHD. Gene therapy follow-up is therefore likely less onerous, focusing only on disease resolution and monitoring for malignancy and long-term complications.

Table 5
Evidence Based Assessment of Accessibility of allogeneic HCT and autologous gene therapy

Location	• Both allogeneic HCT and autologous HCT after genetic modification require specialized centers for stem cell collection and processing, therefore HCT is more feasible and practical in developed countries
Follow-up	• Patients require optimized long-term healthcare monitoring of nearly every organ system to ensure post-transplant well-being and early recognition of late complications. • Gene therapy follow-up is likely to be less onerous given lack of allogeneic specific complications, therefore gene therapy follow-up may ultimately be more feasible for developing countries provided the follow-up care is minimal. • Though the complexity of gene therapy requires a specialized center, the reduced monitoring required post-HCT may allow patients to be treated in a centralized center but return to their local center for monitoring. • Both allogeneic HCT and gene therapy require continued monitoring for the development of malignancy post-HCT
Eligibility	• In the current format of using chemotherapy, allogeneic HCT is more feasible for patients with pre-existing co- morbidity as reduced toxicity conditioning regimens are available • Myeloablative therapy, and by extension gene therapy in its current form, is limited by the short and long-term toxicities of conditioning • Gene therapy eligibility is dependent on the ability to collect a sufficient number of CD34+ cells to generate a gene therapy product

Table 6
Evidence Based Assessment of Cost of allogeneic HCT and autologous gene therapy

Cost of allogeneic HCT	• The cost of allogeneic HSC is dependent on donor source, preparative regimen (myeloablative vs. non-myeloablative) and the risk for post-transplant complications • In the U.S. and Europe gene therapy is more expensive than allogeneic HSC due to increased manufacturing demands
Cost of gene therapy vs. allogeneic HCT	• Gene therapy may ultimately be the more feasible for developing countries provided the follow-up care is minimal. This may allow patients to be treated in a centralized center but return to local center for monitoring • While upfront costs of either approach may be high, quality-adjusted life-years gained and potential to reduce overall lifetime healthcare costs may render curative therapy cost-effective • To make curative therapies financially feasible, there is a need to shift from fee-for-service to a value-based payment system

Patients require optimized long-term health care monitoring of nearly every organ system to ensure post-transplant well-being and early recognition of late complications. A consensus summary reviewing late effects after HSCT in children with SCD and thalassemia [107] has now been followed up with comprehensive late effects screening guidelines [108]. Specifically with regard to patients with TDT, the guidelines focus on organ toxicities associated with iron overload and the susceptibility to hepatic veno-occlusive disease. For patients with SCD, monitoring of the central nervous system as well as cardiac, pulmonary and renal systems, in addition to continued management of chronic pain, is critical.

For both TDT and SCD, hypogonadism and risk of infertility are high both pre- and post-HSCT as a result of iron overload, HU use and recurrent priapism in SCD as well as HSCT conditioning regimens. Risks are impacted by the stage of pubertal development at HSCT [31,109,110] and the preparative regimen utilized [111,112]. Presumably, gonadal dormancy and shorter exposure to iron overload contribute to better preservation of fertility when HSCT is performed early in life [113]; however, when not possible, hormonal therapy may be of benefit [112,114–117].

Patient eligibility

HSCT morbidity is significantly influenced by the preparative conditioning regimen regardless of whether allogeneic or autologous HSCT methodology is used. Therefore, the broad applicability of either curative therapy is limited by the patient's disease status and ability to undergo conditioning.

Unlike current allogeneic HSCT protocols, almost all gene therapy studies utilize myeloablative conditioning to maximize marrow repopulation with genetically modified cells (exception, NCT02186418). In the allogeneic setting, 20–25% donor myeloid chimerism is sufficient to reverse the sickle phenotype in SCD [18,19], and chimerism as low as 10% has been reported in TDT [20]; therefore, RIC is possible and may be preferred, though early and late graft failure remains a challenge. RIC allows access to curative therapies for a greater number of patients who may have substantial comorbidities and be otherwise unable to tolerate myeloablation.

There are also additional patient factors that may limit either therapy. A history of antibodies directed against either donor HLA or red cell antigens may preclude a patient from undergoing haploidentical HSCT because of the increased risk of graft rejection and pure red cell aplasia post-HSCT. Desensitization approaches such as plasmapheresis combined with anti-B-cell antibodies (rituximab) and immune modulators (bortezomib) have been used to overcome these concerns in some cases [118,119]. With regard to gene therapy, success is dependent on safely obtaining a sufficient quantity of autologous SCD patient HSCs to enable lifelong engraftment. In patients with SCD, steady-state BM harvesting is associated with suboptimal HSC quality and yield [91], and PBSC mobilization with granulocyte colony-stimulating factor is contraindicated [120–122], though single-agent plerixafor mobilization appears to be safe and effective [88–90,93]. Some patients may be unable to mobilize a sufficient number of CD34+ cells following plerixafor administration to generate a gene therapy product. It is likely that these patient factors will be less of a concern in pediatric patients, who have better overall organ function and less exposure to RBC antigens from a lifetime of RBC transfusions, and this is a compelling reason to offer these therapies earlier in the disease course.

Cost

The evidence-based assessment regarding the cost of allogeneic HSCT versus gene therapy in hemoglobinopathies takes into consideration the cost of standard of care versus allogeneic HSCT versus gene therapy and is summarized in Table 6.

Cost of standard care for Hb disorders

Both TDT and SCD are chronic diseases with high health care utilization; therefore, management becomes more costly over time. Costs for patients with TDT are associated with regular transfusions, iron chelation therapy and monitoring and management of complications, including iron overload and infections [6]. SCD is a chronic, debilitating condition that causes increased organ damage over time. In the US, SCD accounts for an estimated $1.6 billion per year in health care

costs [123]. For a patient with TDT who survives to age 50, total health care costs are estimated to be $720,201 (£483,454) [124], and total health care costs are estimated to exceed $8 million in a patient with SCD [125]. When addressing health care costs, however, hidden costs are often not factored into health care estimates, including loss of wages due to frequent health care visits, unemployment among patients and parents and reduced quality of life. Although advances in iron chelation in TDT, maximizing HU therapy in SCD and the discovery of new therapeutics improve disease management, a greater focus on curative approaches for these diseases might also represent a suitable strategy for reducing personal lifetime health care costs and improving quality of life.

Cost of allogeneic HSCT in Hb disorders

In the US, the majority of HSCT costs (>75%) for both autologous and allogeneic patients occur during the initial transplant hospitalization and are estimated to be $100,000 for autologous HSCT and $200,000 for allogeneic HSCT during the first 100 days post-HSCT [126]. Average HSCT cost per patient with TDT is $251,723 (€215,571) [127], though significantly lower costs have been approximated in resource-limited countries [53]. Median HSCT cost per patient with SCD is estimated at $467,747 (range, $344,029–799,219) [128], though this may be nearly 50% lower in patients who receive a non-myeloablative regimen [129]. Such costs therefore limit these therapies to developed countries and countries with higher gross national incomes, governmental health care expenditures and team densities [130]. Nevertheless, resource-limited settings have an increased interest in developing HSCT programs given the potential ability to cure chronic, debilitating and expensive diseases such as TDT and SCD. Although the upfront costs of HSCT are high, chronic diseases exert their deleterious effects over the long term, and interventions that seek to change the course of the disease may be economically justified [129]. Ultimately, the quality-adjusted life-years gained for the patient and the potential to reduce overall lifetime health care costs may render curative therapy cost-effective [131].

Comparison of projected gene therapy costs in the US and Europe versus allogeneic HSCT

Costs for gene therapy are less certain and suggested to be as high as $900,000–2.1 million [132], severely limiting real-world applicability. In the current market, the majority of expenses for gene therapy occur in the pre-transplant period given the complexity of DP collection, manufacture and compliance with safety and regulatory standards in addition to the more intensive preparatory patient management leading up to HSCT. During HSCT, total average medical costs excluding vector costs have been shown to be relatively homogeneous among patients with TDT treated with either allogeneic HSCT (£173,497) or gene therapy (£188,334) [127]. Patients treated with gene therapy have lower costs in the follow-up period owing to fewer infectious complications, treatments, imaging, outpatient care and inpatient admissions. Gene therapy patients have fewer productivity losses, experience fewer complications and hospital admissions and have a shorter length of hospital stay, but gene therapy costs on average an additional £300,000–400,000 per patient. Nearly half of this total cost is due to expenses associated with the vector, whereas nearly half of the cost of allogeneic HSCT is due to outpatient care and inpatient admissions. An increase in manufacturer competition and evolution of practices should decrease these manufacturing costs. Increasing the number of patients treated and factoring in age and weight at the time of collection/manufacture could further impact manufacturing costs. Finally, gene editing techniques that utilize more readily available and inexpensive editing tools and eliminate the costly vector component may reduce the overall expenditure and increase the potential broader feasibility of gene therapy.

To justify the additional costs associated with gene therapy, comparing clinical effectiveness with established curative options, assessing value and determining affordability are necessary [133]. Gene therapy trials are non-randomized, single-arm trials using historical cohorts for comparison; therefore, there may be an overestimation of benefit [134]. The assessment of value is similar for allogeneic HSCT versus gene therapy, as curative therapies may be valued more highly by society than treatments that reduce but do not eliminate ongoing costs of patient support and management of chronic comorbidities. Payers typically focus on health gains for the patient and net direct costs to the health system when evaluating payment for therapy, though this does not take into account hidden patient costs. For patients with TDT and SCD, this equates to easily measurable outcomes such as a reduced need for transfusions, hospitalizations, emergency room visits, prescription medications such as treatment for iron overload or acute and chronic pain and health care utilization overall. This does not, however, account for improved quality of life, steady employment, increased wages or other productivity gains. To assess the full financial impact, long-term savings, hidden costs, quality-adjusted life-year adjustments and productivity gains and losses should be included in affordability considerations. Based on the initial pricing experience with gene therapy in Europe, with an estimated upfront treatment price of over US$1 million per patient, the cumulative budget impact is not sustainable. According to health policy experts, “The cumulative budget impact at that price could rise to US $3 trillion, as much as is currently spent in a year on all health care in the USA” [133]. Although there may be a cost benefit to gene editing strategies over vector-based therapies, there are too little data to suggest a clear benefit of one gene therapy methodology over another at this time. Having multiple gene therapy strategies investigated is of utmost benefit to patients who are in search of curative therapies and whose options are limited by donor selection. Data from multiple methodologies maturing simultaneously will help to identify whether there is a superior method, as identified by measurable outcomes, sustainability of therapy (Hb production) over time and safety, all while simultaneously bringing competition into the manufacturing market.

Ultimately, the gene therapy cost model may need to shift from fee-for-service to value-based payment systems [135]. One proposal suggests that 80% of the cost of gene therapy is put at risk to prove the value of its treatment; after an initial upfront charge, DP manufacturers would get paid only if the one-time infusion continued to benefit patients. Recently, the US Centers for Medicare & Medicaid Services presented a proposal to ease value-based payment models for gene therapies, increasing payer price negotiating power and the ability to arrange payment based on outcome over quantity [136]. Other proposed mechanisms for handling affordability include reinsurance, consumer loans, third-party financing, manufacturer-managed financing and government financing, though many of these remain untested and impractical [133]. In the current form, the financial burdens of gene therapy preclude the inclusion of this treatment as a realistic option for a cure available to all.

Discussion

TDT and SCD are growing global health disorders with limited disease-modifying therapies. Both TDT and SCD can be cured by HSCT, with recent evidence suggesting that gene modification of autologous HSCs could become a universal cure. Allogeneic transplantation is limited by donor selection, morbidity and mortality related to transplant conditioning, GVHD and graft rejection, whereas significant concerns regarding long-term safety, efficacy and cost limit the broad applicability of gene therapy. Patient-specific factors and location further limit the widespread applicability of curative therapies.

Therefore, strategies that aim to improve patient outcomes, reduce disease morbidity and dramatically reduce costs are needed to improve the lives of millions of patients with hereditary hemoglobinopathies.

Declaration of Competing Interest

JJB is a member of the International Society for Cell & Gene Therapy Stem Cell Engineering Committee and consults for Avrobio, BlueRock Therapeutics, Race Oncology, Advanced Clinical, Omeros, Sanofi and Medexus Pharmaceuticals. AAA served on the safety monitoring committee for Sangamo Therapeutics. CB consults for Zodiac Pharmaceuticals, Amgen and Novartis. SP receives support for the conduct of clinical trials through Memorial Sloan Kettering from AlloVir, Atara Biotherapeutics and Jasper Therapeutics and is the inventor of intellectual property related to the development of a third-party, virus-specific T-cell program, with all rights assigned to Memorial Sloan Kettering.

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