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HOW I APPROACH

How I approach disease-modifying therapy in children with sickle cell disease in an era of novel therapies

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Abstract

Finally,after decades of stagnation, the therapeutic landscape for sickle cell disease (SCD) is changing with an increasing number of novel *therapeutics*. Hydroxyurea remains the primary disease-modifying therapy and, when started early in life with maintenance of an optimal dose, can reduce many SCD-related complications. To complement hydroxyurea, there are a growing number of pharmacologic options with additional efforts focused on the development and optimization of curative therapies. Here, we review current treatment options and provide recommendations as to how to approach the treatment of children and adolescents within this evolving therapeutic landscape to allow for full and healthy lives.

KEYWORDS
hydroxyurea, pediatrics, sickle cell disease, therapy

1 | INTRODUCTION

Sickle cell disease (SCD) has been well-characterized for over 100 years, with the first clinical report published in 1911 and its description as the "first molecular disease" in 1949.[1,2] Despite this long scientific history, progress toward disease-modifying therapies has been stagnant, likely due in part to the fact that SCD affects primarily minority and marginalized Black populations in high-resource nations and those living in low-resource settings of sub-Saharan Africa and India. Over the past several decades, the implementation of newborn screening for SCD with tight linkage to clinical care and the initiation of prophylactic penicillin have substantially reduced early mortality in high-income settings.[3] However, these preventive measures do not reduce hemoglobin S (sickle hemoglobin, HbS) or prevent the myriad of inevitable and unrelenting complications of SCD. Prior to the discovery that hydroxyurea can modify the clinical course through the induction of fetal hemoglobin (HbF),[4] the only true disease-modifying therapy was blood transfusion. Hydroxyurea is now well-established as the primary disease-modifying therapy for SCD with over 35 years of experience demonstrating safety and efficacy.[5–7] Treatment options have only recently begun to expand with Food and Drug Administration (FDA) approval of three new pharmacologic therapies since 2017, beginning with L-glutamine (Endari) and followed by the humanized monoclonal antibody crizanlizumab (Adakveo) and the hemoglobin-binding small-molecule voxelotor (Oxbryta). In addition, several promising genetic approaches targeting a cure for SCD are being evaluated in teenagers and adults.[8–10] Here, we review these therapies for SCD and provide recommendations as to how to approach the treatment of children and adolescents within this evolving therapeutic landscape.

2 | WHOM TO TREAT

The overarching sickle cell disease term, defined as SCD here, encompasses a broad group of heterogenous disorders with the common feature of the predominance of HbS. Sickle cell anemia (SCA) refers to the most severe genotypes, primarily but not limited to HbSS and HbSβ^0 thalassemia. The SCA genotypes are characterized by the early onset of profound and chronic hemolytic anemia, endothelial activation, and

Abbreviations: AE, adverse event; CTT, chronic transfusion therapy; EFS, event-free survival; FDA, Food and Drug Administration; GVHD, graft-versus-host disease; HbF, fetal hemoglobin; HbS, hemoglobin S (sickle hemoglobin); HIV, human immunodeficiency virus; HSCT, hematopoietic stem cell transplantation; MSD, matched sibling donor; MTD, maximum tolerated dose; NHLBI, National Heart, Lung, and Blood Institute; OS, overall survival; RBCs, red blood cells; SCA, sickle cell anemia; SCD, sickle cell disease; TCD, transcranial Doppler; VOE, vaso-occlusive episode.

TABLE 1 Currently approved medications

Agent	Mechanism of action	Dosing/administration	FDA approval		Response assessment	Estimated cost[a]
			Genotype	Age (years)		
Hydroxyurea	Induction of HbF	Oral (capsules, dissolvable tablets, or compounded liquid) daily, begins at 25 mg/kg and increases to MTD	SCA (HbSS or HbSβ^0 thalassemia)	≥2	CBC, reticulocyte count, %HbF, F cells	~$150 for 30-day supply[b]
L-glutamine (Endari)	Antioxidant	Oral, 10–30 g twice daily (available as 5-g powder packs)	All genotypes	≥5	Clinical	$2904–$8712 for 30-day supply[c]
Crizanlizumab (Adakveo)	P-selectin inhibitor	Intravenous infusion, 5 mg/kg every 2 weeks × 2 doses, followed by 5 mg/kg every 4 weeks	All genotypes	≥16	Clinical	$8549 for every 4-week dosing[d]
Voxelotor(Oxbr	Inhibition of HbS polymerization	Oral (tablets), 1500 mg once daily	All genotypes	≥12	Hemoglobin level	$12,500 for 30-day supply

Abbreviations: CBC, complete bood count; FDA, Food and Drug Administration; HbF, fetal hemoglobin; HbS, sickled hemoglobin; MTD, maximum tolerated dose; SCA, sickle cell anemia.

[a]Costs are out-of-pocket expenses and do not take into account insurance coverage.

[b]Cost of one 500-mg tab = $1.64, dosing for 60-kg adult, 25 mg/kg (1500 mg) daily.

[c]Cost of one 5-g packet Endari = $24.20.

[d]1 ml of 100 mg/10 ml concentration = $284.98, dosing for 60-kg adult, 5 mg/kg (300 mg) every 4 weeks.

microvascular occlusion from polymerization of HbS and subsequent sickling of red blood cells (RBCs). Although there is significant interpatient variability in the timing or severity of overt clinical manifestations, SCA is unrelenting and if left untreated leads to life-threatening acute and chronic complications, including increased risk of overwhelming bacterial infection, frequent painful vaso-occlusive episodes (VOE), and progressive dysfunction of virtually all organs, which in combination, reduce both the quality and length of life for affected individuals. With the decline in HbF, the hemolytic anemia and associated chronic organ damage of SCA begin as early as the first year of life, usually before more overt clinical manifestations emerge. We strongly recommend that all patients with SCA receive disease-modifying therapy as early as possible; the initiation of hydroxyurea at 6–9 months of age should be the *standard of care* for all infants with SCA genotypes. While the 2014 National Heart, Lung, and Blood Institute (NHLBI) guidelines recommend offering hydroxyurea to children beginning at 9 months of age due to inclusion criteria of the BABY HUG study, some patients develop more severe hemolytic anemia and clinical symptoms as early as 6 months of age. For this reason, it is our practice to offer hydroxyurea to children with SCA beginning at 6 months of age to protect end organs and prevent rather than wait for the manifestation of potentially serious and life-threatening complications.[11] Further, our recommendation remains the same throughout the lifespan, such that no patient with SCA should be left untreated.

Individuals with non-SCA genotypes, including but not limited to HbSC and HbSβ^+ thalassemia, typically have a higher baseline hemoglobin, a less severe hemolytic anemia, and dense, poorly deformable RBCs. Much of the clinical pathophysiology stems not from hemolysis, but rather hyperviscosity related to these factors.[12–14] The clinical course for non-SCA genotypes is generally mild during early childhood, but can be tremendously variable as patients age into adolescence and adulthood with increased frequency of painful VOE, chronic organ damage, and poor health-related quality of life. In contrast to its clear hematologic and clinical benefits for SCA, hydroxyurea has a less predictable degree of HbF induction and variable efficacy in reducing clinical complications for patients with non-SCA genotypes, although data are limited, and this remains a significant knowledge gap that warrants further investigation.[11] Several novel therapeutic agents have been studied in patients with non-SCA genotypes and will be specifically discussed below. In contrast to SCA, in which treatment should be universal, currently, the decision to treat individuals with non-SCA genotypes should depend upon the types, frequency, and severity of clinical symptoms.

3 | CURRENTLY APPROVED MEDICATIONS

3.1 | Hydroxyurea

Hydroxyurea is a once daily oral medication, with over 35 years of evidence demonstrating its ability to reduce nearly all acute and many chronic complications of SCA (Table 1). There are several salutary effects of hydroxyurea, but the primary hypothesized mechanism by which hydroxyurea provides clinical benefits is through the induction of HbF, the most potent inhibitor of HbS polymerization.[15] The Phase III Multicenter Study of Hydroxyurea (MSH) and the Pediatric Hydroxyurea Phase III Clinical Trial (BABY HUG) demonstrated hydroxyurea's ability to reduce the frequency of painful VOE, which resulted in it

becoming the first FDA-approved medication in adults (1998) and children (2017) with SCA.[5,7] The 2014 NHLBI evidence-based clinical guidelines recommend "offering hydroxyurea to infants 9 months of age and older, children, and adolescents with SCA, regardless of clinical severity."[11] While the labeling of hydroxyurea as a chemotherapy agent due to its historical use to treat cancer and data from early in vitro and animal studies using extreme concentrations of hydroxyurea has resulted in significant notoriety, there is now sufficient real-world clinical evidence to strongly support our belief that the benefits significantly outweigh any putative risk.[16–18] However, further studies investigating the long-term effects of hydroxyurea upon reproductive and other organs are needed, particularly in children who began hydroxyurea at an early age.[19] Importantly, as we have demonstrated, the conversation about hydroxyurea must begin early with its introduction as a medication prescribed to prevent acute and chronic complications of SCA and to allow for a high quality of life.[20] These conversations must also directly address the misinformation that parents often find from internet searches, social media, or older members of the sickle cell community. This contrasts with the previous approach, which cautiously introduced hydroxyurea as a medication with an unknown side effect profile used only in the setting of frequent or severe complications. In our experience, this change in the overall approach and discussion of hydroxyurea, supported by decades of real-world clinical experience and data from high-quality clinical trials,[5–7] has resulted in less skepticism and improved acceptance of and adherence to hydroxyurea therapy.[20]

The decision to prescribe hydroxyurea is not static and requires careful ongoing monitoring of both adherence and dose to optimize effect. Based on our experience, we recommend consideration of the following when prescribing hydroxyurea:

1. *Age of initiation*: Due to the early development of disease manifestations even prior to the NHLBI guidelines' recommendation of 9 months,[11 and a] more robust HbF induction when started in infancy,[21] we typically begin hydroxyurea between 6–9 months of age as the standard of care for infants with SCA.
2. *Starting dose*: Based on several recent trials having demonstrated safety in starting hydroxyurea at higher than traditional dosing (20 mg/kg/day),[21–23] we now begin children at 25 mg/kg/day to optimize hydroxyurea's effect more quickly.
3. *Dose adjustments and laboratory monitoring*: The early studies of hydroxyurea involved starting with a standard dose and then increasing to target mild myelosuppression at the maximum tolerated dose (MTD).[5,6] In addition, despite evidence that fixed dosing is safe and effective in low-resource settings,[24,25] a recent trial in sub-Saharan Africa comparing fixed to MTD-based dosing was stopped early due to the superiority of MTD-based dosing in reducing SCD-related complications.[22] Thus, in accordance with the NHLBI guidelines, we monitor complete blood counts (CBC) to determine dose adjustments monthly until an optimal dose (MTD) is reached, followed by every 3–6 months. In addition, routine weight-based dose adjustments are critical to maintain a stable milligram per kilogram dose; the availability of compounding pharmacies for a liquid hydroxyurea formulation allows for flexibility in dose titration (Figure 1). In contrast to concerns regarding dose-limiting neutropenia,[6,7,26] and although limited to our single-center experience, we have found no increase in bacteremia even after lowering our dose-limiting absolute neutrophil cutoff to 750/μl from the NHLBI guidelines' recommendation of 1250/μl.[11,20]
4. *Fetal hemoglobin target*: Although an HbF of 20% is often the treatment target for hydroxyurea therapy,[27] higher HbF levels provide increased protection against HbS polymerization and RBC sickling. As opposed to overall %HbF, it may be helpful to also assess the distribution of HbF among RBCs (known as F cells), which is becoming an increasingly available clinical test. Quantitation of F cells can provide more comprehensive information about the hydroxyurea effect.[28] A target of HbF ≥30%, which corresponds to a near-pancellular HbF distribution across RBCs (>70%–80% F cells), should prevent HbS polymerization, RBC sickling, and reduce the frequency and intensity of most complications of SCA.[29,30] Importantly, we do not stop hydroxyurea dose titrations at a certain %HbF, but instead continue base dosing upon hematologic parameters (absolute neutrophil count, absolute reticulocyte count, platelet count) to achieve optimal laboratory and clinical benefits.
5. *Non-SCA genotypes*: Although no large, prospective trial has been completed, it is our clinical practice- and expert opinion-based recommendation to offer hydroxyurea on a trial basis for individuals with non-SCA genotypes (primarily HbSC and HbSβ^+ thalassemia) if they suffer from frequent pain or other clinical complications,[31,32] recognizing that laboratory values are not necessarily accurate markers of response in these patients. We optimize dosing to also target mild myelosuppression with the same strategy as discussed for SCA genotypes. Instead of using HbF as for SCA genotypes, we based the response to hydroxyurea on the ability to reduce or prevent the clinical complications leading to hydroxyurea use, usually painful VOE.
6. *Medication adherence*: In our experience, the primary barrier to achieving benefit with hydroxyurea therapy is suboptimal medication adherence; we recommend discussing and reviewing this at each clinical visit, including patient-reported adherence and laboratory trends. Given the complexity of factors related to medication adherence, if available, we recommend the inclusion of pediatric psychologists as necessary to address barriers and to develop strategies to improve adherence.

3.2 | L-glutamine

Oxidative stress is an important component of the pathophysiology of SCD as sickled RBCs have an increased number of reactive oxygen species compared to normal RBCs.[33,34] Glutamine is a conditionally essential amino acid in catabolic states, including SCD, and is required for the synthesis of glutathione and for other antioxidant pathways. Thus, the rationale for glutamine supplementation in clinical practice is as a mechanism to augment antioxidation in SCD.

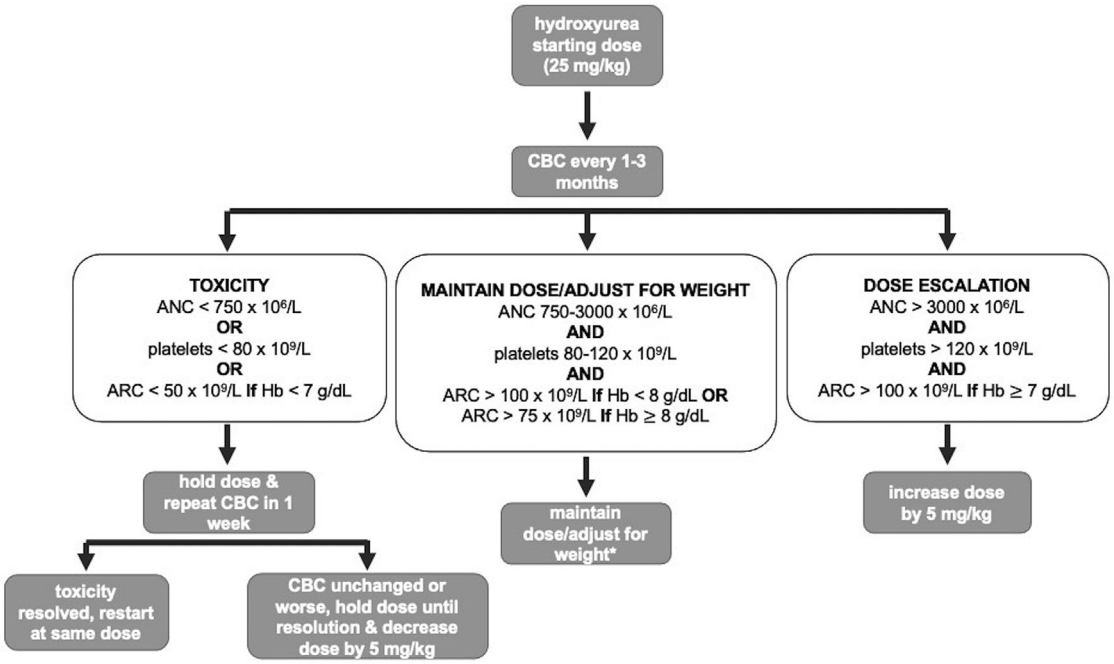

FIGURE 1 Hydroxyurea dose-titration algorithm. Guide for hydroxyurea dose titration and weight adjustment based on complete blood count (CBC) results. *If the optimal mg/kg dose (MTD) has decreased by more than 2.5 mg/kg due to weight gain since the last visit, adjust the absolute dose (mg) to maintain a stable MTD (mg/kg); for example, if a child demonstrated excellent effect with ANC in the target range at a dose of 200 mg when she weighed 8 kg, her optimal (or maximum tolerated) dose is 25 mg/kg. If she gains weight by the next visit to 12 kg and labs do not demonstrate toxicity, adjust the dose to maintain 25 mg/kg. In this case, we would "adjust the dose for weight gain" to 300 mg to maintain a 25 mg/kg dose. ANC, absolute neutrophil count; ARC, absolute reticulocyte count; g/dl, grams per deciliter; mg/kg, milligrams per kilogram; /L, per liter

L-glutamine (Endari), available in a powder formulation taken twice daily, received FDA approval for adults and children (≥5 years of age) with SCD based on the results of a phase III randomized placebo-controlled trial, which determined that individuals on L-glutamine had fewer SCD-related pain crises than those on placebo (median of 3.0 vs. 4.0 over 48 weeks, $p = .005$) and a longer time to first VOE (84 vs. 54 days, $p = .02$).[35] The study found no differences in changes in laboratory parameters between the cohorts. Given the complexity of the antioxidative system in RBCs, it is still unclear as to the relative importance of glutamine within this milieu. In addition, there are currently no available biomarkers to assess response to glutamine supplementation, nor studies for optimal dosing. A recent review of L-glutamine in SCD suggested studying the additive benefits of its supplementation to the proven effects of hydroxyurea.[36] Further investigation of the pharmacokinetics, pharmacodynamics, and hematologic effects of L-glutamine as a disease-modifying therapy for SCD is warranted. Based on current evidence, we recommend hydroxyurea as the backbone of therapy, but that the addition of L-glutamine can be considered for those with frequent pain despite appropriate hydroxyurea adherence.

3.3 | Crizanlizumab

The humanized monoclonal antibody crizanlizumab (Adakveo) binds to P-selectin, inhibiting its interaction with P-selectin glycoprotein ligand 1 and thereby reducing leukocyte, platelet, erythrocyte, and endothelial adhesion, important pathophysiologic components leading to acute VOE.[37–39] The medication received FDA approval in November 2019 to reduce the frequency of VOE for adults and pediatric patients (>16 years of age) with any SCD genotype. The medication is administered intravenously initially every 2 weeks for the first month and then monthly thereafter. Approval was based on the results of the SUSTAIN trial, a phase 2, multicenter, randomized, placebo-controlled trial to assess crizanlizumab's safety and efficacy in children and adults ages 16–65 years with two to 10 VOE within the prior 12 months.[40] High-dose crizanlizumab (5 mg/kg) was associated with a significant reduction in the frequency of (median 2.98 crises per year vs. 1.63, $p = .01$) and an increase in time to first VOE (4.07 months vs. 1.38 months, $p = .001$) compared to placebo. The study also reported no difference in adverse events (AEs); subsequent studies have further demonstrated its safety and efficacy with no additional AEs aside from headache and pyrexia, as reported in the original SUSTAIN trial.[40,41] However, as of October 2020, Novartis has received 22 reports of acute pain or other systemic complications developing within minutes of the infusion of the first or second dose, possibly consistent with the complement activation-related pseudoallergy reaction reported with other monoclonal antibodies,[42] which prompted the company to release a postmarketing safety statement and to create a website with updated safety information.[43] While there appears to be benefit in the reduction

TABLE 2 Indications for transfusion in SCD

Transfusion type and timing	Indications	Complications and disadvantages
Acute transfusions		
Simple transfusion	Acute anemia with concern for developing ACS[a] Acute anemia in setting of persistent VOE[b] Acute splenic sequestration Viral-induced aplastic crisis[c] Preoperative transfusion with target Hb 10–12 g/dl	Risk for transfusion reactionMinor RBC antigen exposure
Erythrocytapheresis(RBC exchange transfusion)	Acute strokeACS[a] Other serious acute illness or clinical instability	Need for central access acutelyMinor RBC antigen exposure
Chronic transfusion therapy		
Simple transfusion ± phlebotomy or erythrocytapheresis	Primary stroke prophylaxis due to abnormal transcranial Doppler ultrasound Secondary stroke prophylaxis for clinically overt cerebrovascular accidents Frequent pain/complications with suboptimal oral medication adherence Pregnancy in women with SCD (as hydroxyurea has not been studied in pregnant women)	Risk for iron overload without concomitant iron chelation or phlebotomy Need for consistent intravenous access/central access Infection risk with central line (erythrocytapheresis) Minor RBC antigen exposure Time requirement (disruption for work/school)

Abbreviations: ACS, acute chest syndrome; g/dl, grams per deciliter; Hb, hemoglobin; RBC, red blood cell; SCD, sickle cell disease; VOE, vaso-oclusive episode.
[a]In the setting of respiratory symptoms (increased work of breathing, hypoxia), a new infiltrate on chest X-ray and/or fever, a simple transfusion may prevent or allay the development of acute chest syndrome; however, if ICU level support is needed, the patient should receive an exchange transfusion to target an HbS <30%.
[b]We recommend against the routine use of transfusion in the setting of an acute drop in hemoglobin without symptoms (i.e., an uncomplicated VOE), but suggest considering transfusion when the VOE is prolonged despite optimization of pain control.
[c]Although the classic viral cause of an aplastic crisis is parvovirus, other viruses can also precipitate transient, severe RBC aplasia, including CMV and EBV.

of painful VOE for some patients, further careful monitoring is necessary. We recommend offering crizanlizumab to patients ≥16 years of age with frequent pain crises interfering with their daily lives. For these patients, we continue to recommend hydroxyurea while receiving monthly crizanlizumab infusions in order to target multiple components of the pathophysiology of SCD.

3.4 | Voxelotor

Voxelotor (Oxbryta) is a once daily, orally bioavailable small molecule that reversibly binds and stabilizes oxygenated hemoglobin, preventing HbS polymerization and RBC sickling.[44–46] The Phase III HOPE trial was a multicenter, randomized, placebo-controlled, double-blind, parallel group trial of patients aged 12–65 years of age with all SCD genotypes. The HOPE trial met its primary end point, with 51% of participants receiving the higher dose (1500 mg) of voxelotor attaining an increase in hemoglobin concentration of at least 1 g/dl at 24 weeks, compared to only 7% in the placebo group.[47] The initial results from HOPE and recently published long-term follow-up, however, have not demonstrated any statistical differences between treatment and placebo groups in the annualized incidence of VOE, nor patient-reported outcome measures such as quality of life.[48] Based on meeting the primary endpoint of increased hemoglobin concentration, voxelotor received accelerated FDA approval for adults and children with all genotypes of SCD at least 12 years old in November 2019. We recommend considering the addition of voxelotor for patients ≥12 years of age who are adherent to hydroxyurea with suboptimal hemoglobin concentrations (<9 g/dl) with careful ongoing hemoglobin surveillance, given that up to 20% of individuals in the HOPE trial treated with the 1500 mg dose experienced a dramatic increase in hemoglobin of >3 g/dl by the full 72 weeks of the study.[48] Although no increase in VOE was reported for those who achieved Hb >12 g/dl, the long-term consequences of an elevated hemoglobin concentration with predominance of HbS on whole blood viscosity and clinical outcomes are still unknown and need further investigation. Given the evidence for the prevention of SCD-related complications with hydroxyurea, which was not seen with voxelotor,[47,48] our personal approach and recommendation is to first prescribe hydroxyurea rather than to replace hydroxyurea with voxelotor as a monotherapy, unless there is a clear contraindication to hydroxyurea. However, voxelotor and hydroxyurea may be an important and effective combination regimen for patients who are on hydroxyurea but are unable to achieve a high hemoglobin concentration.

4 | BLOOD TRANSFUSION

Despite the development of new disease-modifying therapies, blood transfusion remains an essential treatment to manage both acute and chronic complications of SCD (Table 2), with over 90% of adults receiving at least one transfusion during their lifetime.[49] Blood is indicated for numerous acute complications, including severe anemia due to parvovirus-induced aplastic crisis or acute splenic sequestration and other life-threatening events such as stroke and acute chest syndrome. In addition to acute simple transfusion, chronic transfusion therapy

(CTT) remains a primary disease-modifying treatment option to prevent serious long-term (primarily neurologic) complications of SCD. Given the well-described high risk for secondary stroke,[50] all patients with a history of overt stroke should initiate lifelong CTT to maintain HbS <30%. In addition, the STOP trial showed that for children with SCA and abnormal transcranial Doppler ultrasound (TCD) velocities, the risk of stroke was 92% lower in those on CTT with either simple or exchange transfusions.[51] STOP2 revealed the need for indefinite CTT due to the risk for reversion back to an abnormal TCD velocity upon cessation of chronic transfusions.[52] However, the TCD With Transfusions Changing to Hydroxyurea (TWiTCH) trial showed that in the absence of neurovascular abnormalities on MRI/MRA, upon normalization of TCD velocities, and after 1 year of CTT, children can be safely transitioned to hydroxyurea from CTT for primary stroke prophylaxis.[53] There may also be a role for CTT for patients with other serious or life-threatening complications or for those who are unable to tolerate other disease-modifying therapies such as hydroxyurea.

CTT is not without significant adverse effects, which can substantially limit its use. Alloimmunization from minor red cell antigen differences between donor and recipient can occur despite extended matching and can make locating and matching blood difficult.[49] American Society of Hematology (ASH) guidelines for transfusion recommend sending an extended RBC antigen profile ideally by genotype to reduce this risk.[54] Iron overload is the other most common and problematic long-term complication of CTT, requiring routine monitoring of liver iron content and concurrent iron chelation therapy or phlebotomy to reduce this risk. Erythrocytapheresis (RBC exchange transfusion), if available, is recommended as the primary CTT modality for pediatric patients, as it can minimize iron deposition, but requires placement of one or two central venous catheters and specialized equipment and expertise to perform the monthly procedure. Finally, although routine screening has greatly reduced transmission of viral infections via transfused blood, including human immunodeficiency virus (HIV) and hepatitis B and C,[55] transfusion will always have at least some risk of transmission of infection, including bacteria, viruses, and even tick-borne pathogens.[56,57]

5 | POTENTIALLY CURATIVE THERAPIES

5.1 | Hematopoietic stem cell transplantation (HSCT)

The first bone marrow transplant for SCD was completed in 1982 in an individual with HbSS and acute myeloid leukemia, which resulted in the realization that in addition to curing her leukemia, the child no longer had SCD, but sickle trait.[58] Since then, HSCT has been primarily offered as a curative treatment option for those with severe disease, most commonly stroke, or for families who strongly desire a cure.[59] HLA-matched sibling donor (MSD) transplants have had an excellent event-free (EFS) and overall survival (OS) (91% and 93%, respectively),[60] but unfortunately less than 20% of SCD patients have a full HLA-matched sibling.[61] In contrast to the favorable outcomes with MSD transplants, outcomes are significantly worse with other donor sources, with no difference in EFS or OS between matched unrelated, mismatched unrelated, and haploidentical donors.[62] In addition, the effect of HSCT on health-related quality of life is less clear, as reported in a recent preliminary analysis of matched donor transplantation in adolescents and young adults with SCD.[63] An ongoing multicenter phase II trial in adolescents and adults with severe SCA [NCT02766465]) is attempting to address knowledge gaps by comparing HSCT to the standard of care over a 2-year follow-up period with the primary outcome OS and secondary outcomes focused on changes in SCD-related events and functional outcome.[64] The small but present risk for infection, graft rejection, graft-versus-host disease (GVHD), and mortality, as well as unknown long-term complications, limit the uptake of HSCT even for those with donors. In addition, HSCT is expensive and requires significant time away from work for family members during the prolonged transplant period, further reducing the overall number of patients for whom HSCT is a feasible option. However, for the subset of patients with available donors and interest in a curative option, it is important to proceed with HSCT early, as data have shown that for every increase in age by 1 year, the risk for death associated with HSCT increases by 10%.[60] The summative experience of HSCT for pediatric patients with SCD prompted an international series of guidelines recommending transplantation in young children and only those with an MSD or symptomatic disease.[65] In line with these guidelines, we recommend HLA-typing full siblings and discussion of HSCT as a treatment option for families of young children with HLA-MSDs. These discussions, in our center, include referral to the bone marrow transplant team, who can most comprehensively discuss the risks, benefits, and overall experience of HSCT as a curative treatment option. But based on the evidence, we are reluctant to recommend HSCT in those without a fully matched sibling donor.

5.2 | Gene therapy

Given the challenges of HSCT, including a limited donor pool and severe complications, such as GVHD, and its status as a monogenic disorder, SCD is an enticing prospect for gene therapy, which would not require a donor and eliminate the risk of GVHD. There are a number of gene therapy approaches to potentially curing SCD, including the following: (a) the addition of a functional globin, including either a normal beta globin gene or gamma globin to induce HbF production; (b) HbF induction by the inhibition of HbF repressors, particularly *BCL11A*; and (c) direct genetic correction of the SCD mutations.[66] In recent years, two primary methods have moved from preclinical studies to clinical trials: lentiviral vectors and genome editing with clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9). Lentiviral vectors, which are derived from HIV type 1, have the advantages of being able to carry large gene products, transduce nonreplicating cells, and minimize the risk for oncogenesis from random integration into the genome, unlike in earlier viral vectors.[67] More recently CRISPR/Cas9 has made gene therapy human trials an increasingly attainable event. The CRISPR RNA sequence recognizes

a specific genomic DNA sequence and directs the Cas9 endonuclease to create a double-stranded break, allowing for activation of the DNA repair mechanism and either insertions/deletions or homology-directed repair.

There are now several published reports from these studies demonstrating the proof of principle with sustained induction of the nonsickling hemoglobin and significant improvement in symptoms for most patients.[8–10] A recent concern, however, was the development of myelodysplastic syndrome/leukemia in two patients having received lentiviral-based gene therapy with busulfan conditioning. The study sponsor (BlueBird Bio) has halted further study, with an investigation ongoing.[68] In summary, gene therapy is promising with many ongoing preclinical and clinical trials aiming for a safe and effective curative therapy. However, long-term studies demonstrating clear safety and efficacy profiles will be necessary before these therapies are widely recommended for children with SCA.

6 | CONCLUSIONS

After nearly a century of limited options, we are now in an era with multiple new and exciting medications and potentially curative therapies for SCD realistically on the horizon. The increased availability of disease-modifying therapies for SCD has the potential to tremendously change the clinical paradigm and greatly improve the lives of the millions of individuals living with SCD around the world. Hydroxyurea remains the primary disease-modifying therapy for those with the most severe SCA genotypes and with early and aggressive use and careful monitoring of dose and medication adherence, hydroxyurea can ameliorate or even prevent many of the acute and chronic complications. In addition, new agents have been developed that may modulate the clinical course of all SCD genotypes; optimal pharmacotherapy will likely prove to be a combination of agents with complementary mechanisms to address the complex pathophysiology of SCD from different angles. The rapid development of multiple-gene therapy techniques is exciting and suggests that a cure is a realistic possibility for this generation of children born with SCD. Until then, the increasing availability of disease-modifying therapies should be optimized with a goal of allowing children with SCD to live full and disease-free lives.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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