Updates in Sickle Cell Disease Management

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May 22, 2023

Learning Objectives

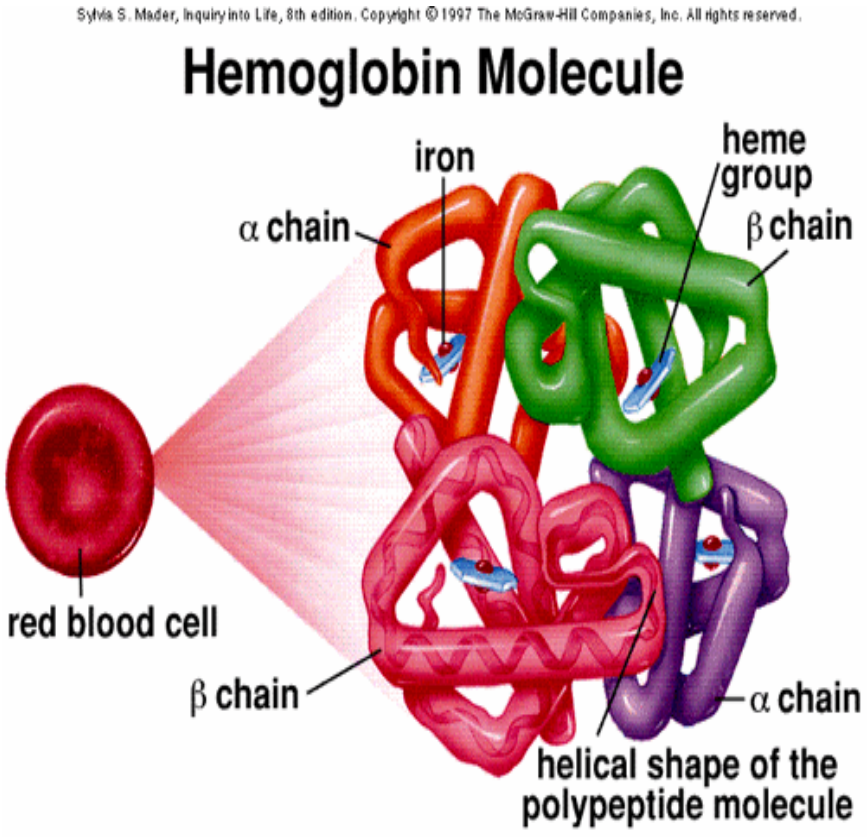
- Review the epidemiology, pathophysiology, and common complications of sickle cell disease
- Demonstrate knowledge of traditional disease-modifying therapies for sickle cell disease
- Explain the mechanisms of action for the emerging therapies for sickle cell disease and describe the appropriate patient population for each

Disclosures

- Has served as an advisory board member for Global Blood Therapeutics

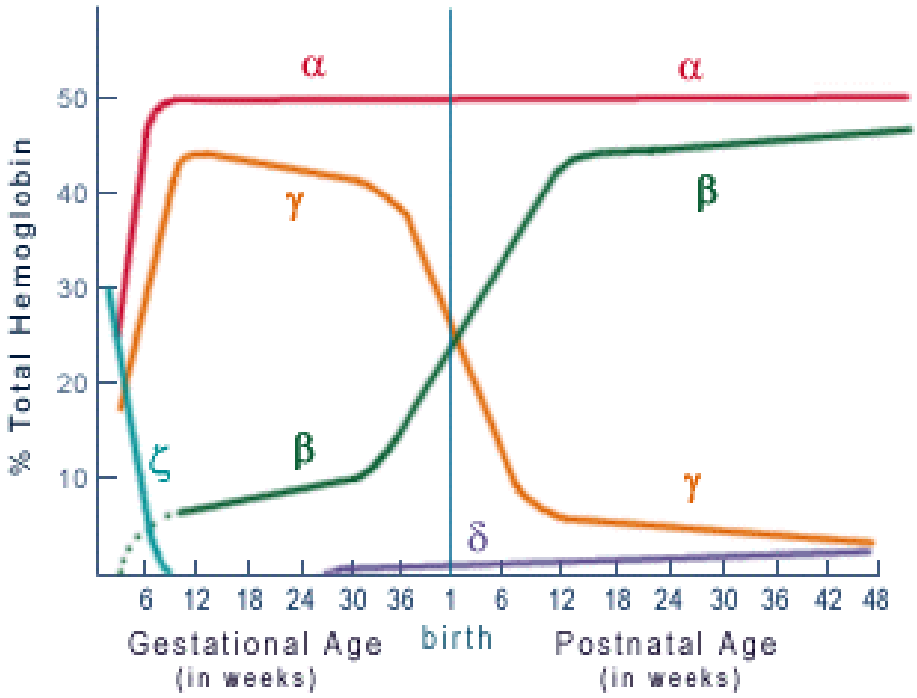
Hemoglobin Structure

- Each erythrocyte has 200-300 million hemoglobin molecules
- Each hemoglobin molecule has 4 globin chains
  - 2 α chains
  - 2 β chains
- Each globin chain contains 1 heme moiety to bind oxygen



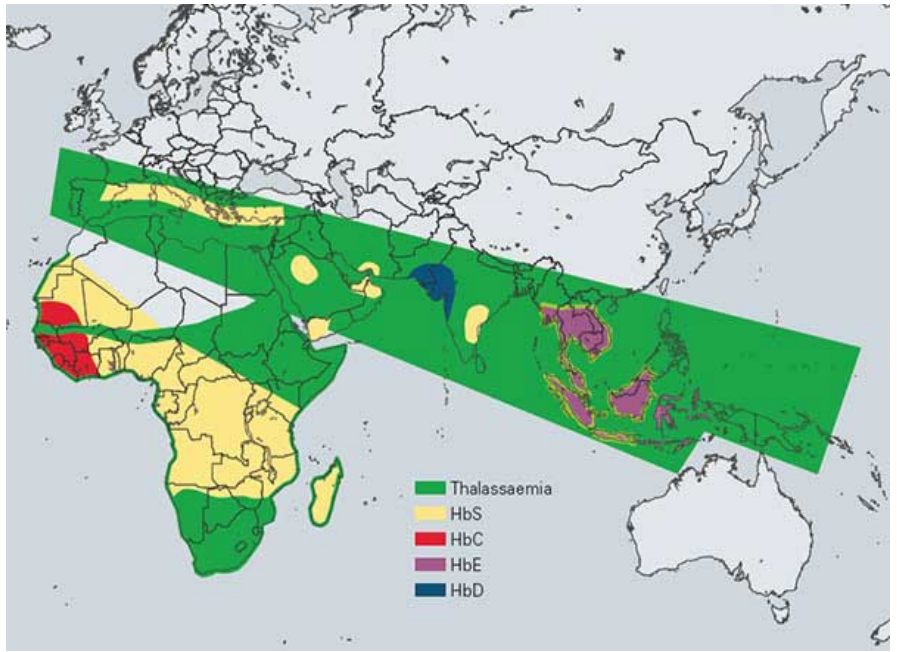
Normal Hemoglobin

- Hemoglobin A: $\alpha_2\beta_2$
- Hemoglobin F: $\alpha_2\gamma_2$
- Hemoglobin A_2: $\alpha_2\delta_2$



Sickle Cell Disease: Epidemiology

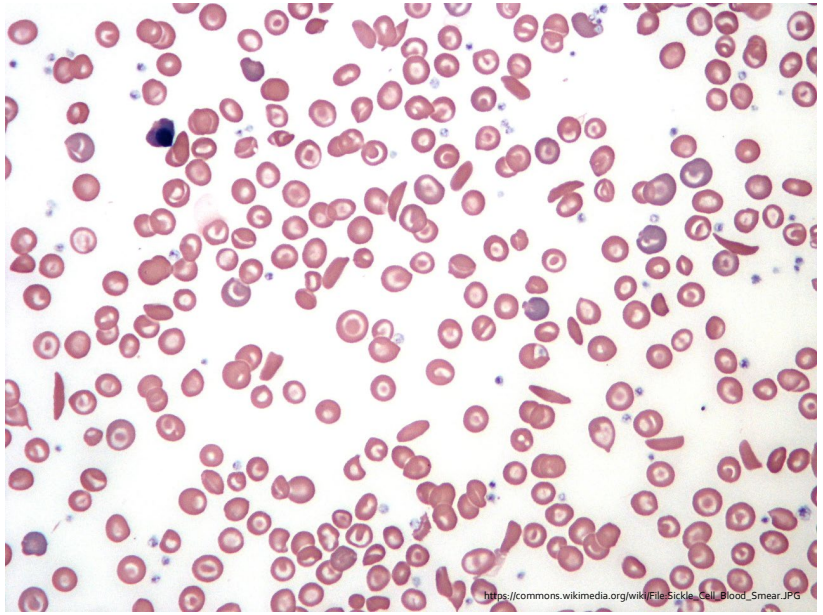
- Autosomal recessive inheritance
- Estimated 100,000 people with SCD in the United States



Pathophysiology

Polymer Formation

- **HbS** is an abnormal β globin protein caused by a single amino acid substitution (Glutamine → Valine) on chromosome 11
- HbS polymers pull cell into sickle shape with deoxygenation
- Triggers of polymerization: dehydration, cold temperatures, hypoxia.
- Inhibitors of polymerization: HbF, alpha thalassemia

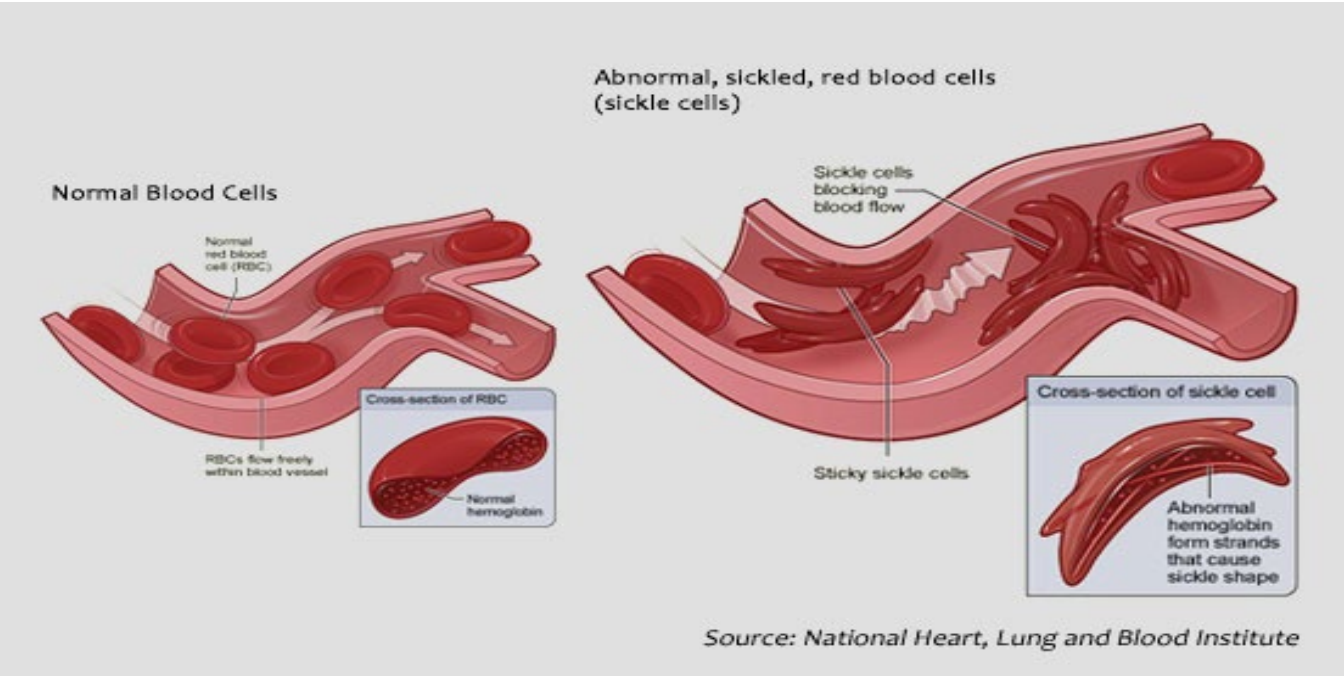


Pathophysiology

- Normal erythrocytes are flexible enough for passage through microcirculation.
- Sickled erythrocytes are rigid and become stuck in the capillaries.
- Tissue is deprived of oxygen, resulting in organ damage over time.

Other contributors to pathophysiology of sickle cell disease:

nitric oxide depletion, inflammation, reperfusion injury



Population-Based Screenings

- Endemic countries – focus on primary prevention
  - Premarital screening for hemoglobinopathy disease/trait
- Non-endemic countries – focus on morbidity prevention
  - Newborn screening for hemoglobinopathies

Newborn Screening for Hemoglobinopathies

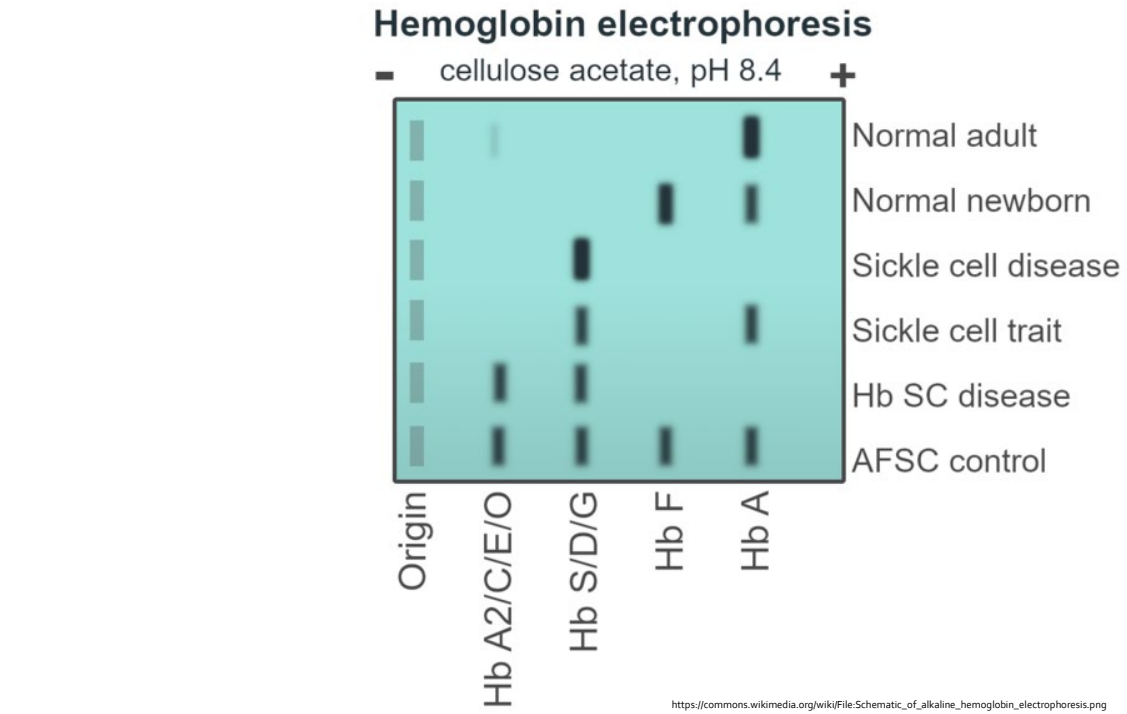
Pattern	Comment
FA	Normal Newborn
FS	HbSS vs. HbSβ^0 thalassemia
FSC	HbSC
FSA	HbSβ^+ thalassemia
FAS	Sickle trait
FAV	Hb variant - trait
FA + Hb Barts	Alpha thalassemia trait

Confirmation: Hemoglobin Electrophoresis

Used to identify and quantify each type of hemoglobin

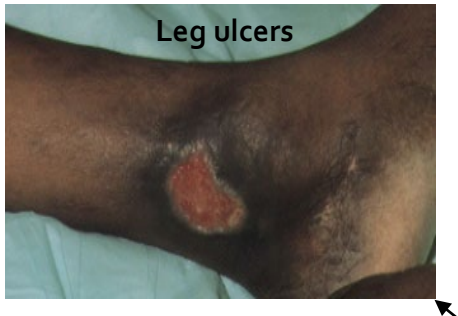
Charged proteins move across agar

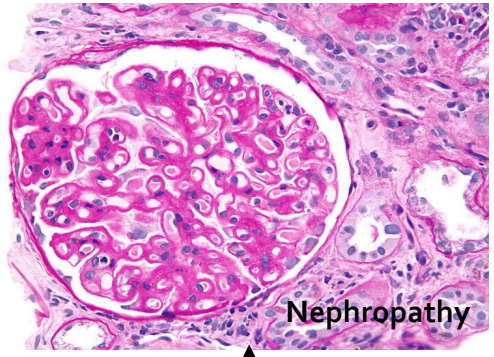
Hemoglobins separate based on charge/weight

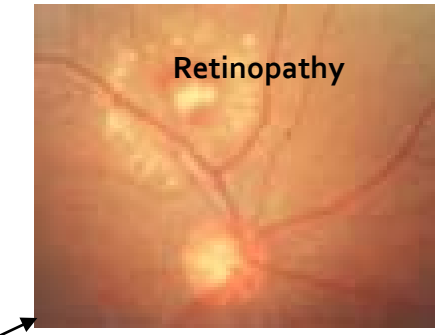


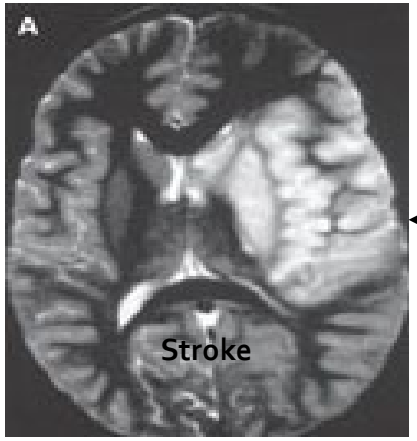
https://commons.wikimedia.org/wiki/File:Schematic_of_alkaline_hemoglobin_electrophoresis.png

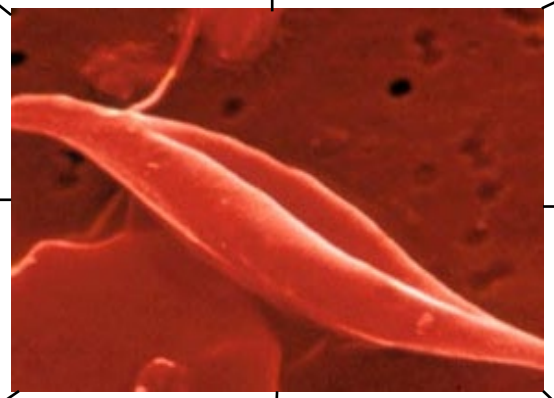
Complications

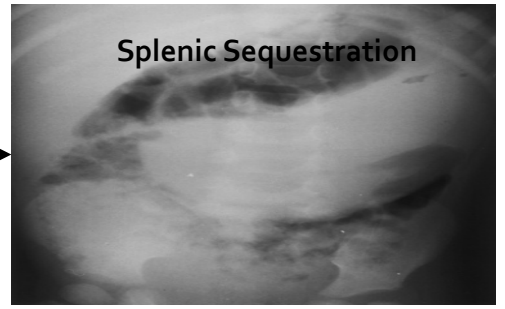


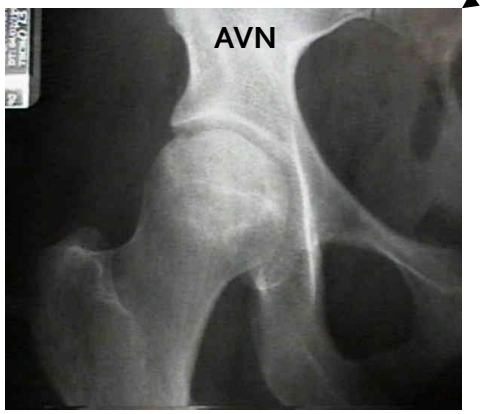


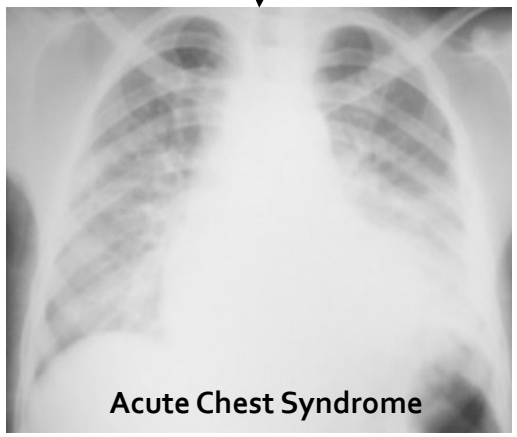












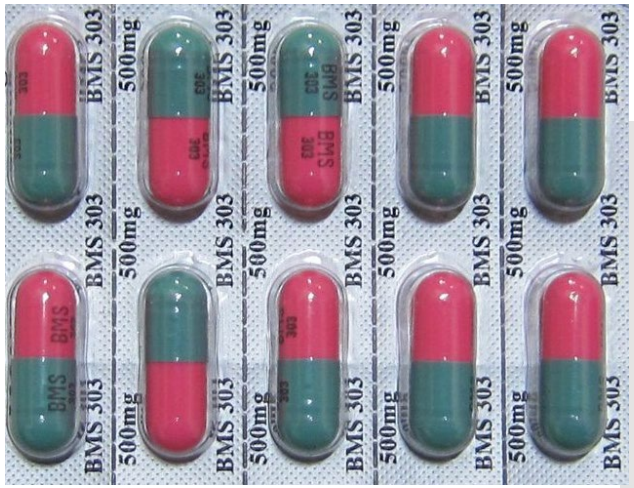
Complications

- **CNS:** CVA, retinopathy, cognitive impairment
- **Pulmonary:** Acute chest syndrome, pulmonary hypertension
- **Gastrointestinal:** Cholecystitis, cholelithiasis, splenic sequestration
- **Genitourinary:** Priapism, pubertal delay, pregnancy complications
- **Renal:** Papillary necrosis, hematuria, nocturnal enuresis, nephropathy
- **Musculoskeletal:** Vaso-occlusive episodes, avascular necrosis
- **Dermatologic:** Leg ulcers

Case Study 1

- A 9 month old male with Hemoglobin FS on newborn screen, confirmed as Hemoglobin SS via hemoglobin electrophoresis, presents to your hematology clinic for establishment of care. He is an only child. His parents request additional information regarding disease-modifying therapies. Of the oral medications available, which is indicated for this child?

Hydroxyurea



- Ribonucleotide reductase inhibitor
- Increases HbF levels
- Decreases circulating leukocytes and reticulocytes
- Alters expression of adhesion molecules
- Increases MCV
- Decreases HbS polymerization, improves cellular deformability
- Metabolization releases nitric oxide, causing vasodilation
- Other advantages: Rapid absorption, excellent bioavilability, once-daily oral dosing.

NHLBI 2014

Hydroxyurea

- 1967: FDA approved as an antineoplastic drug
- 1998: FDA approved for use in adults with sickle cell disease
- 2014: NHLBI published guidelines recommending hydroxyurea for children > 9 months old with sickle cell anemia (BABY HUG study)
- 2017: FDA approved for use in children >2 years with sickle cell disease

Hydroxyurea

ORIGINAL ARTICLE

Effect of Hydroxyurea on the Frequency of Painful Crises in Sickle Cell Anemia

Samuel Charache, M.D., Michael L. Terrin, M.D., Richard D. Moore, M.D., George J. Dover, M.D., Franca B. Barton, M.S., Susan V. Eckert, Robert P. McMahon, Ph.D., Duane R. Bonds, M.D., and the Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia*

May 18, 1995
N Engl J Med 1995; 332:1317-1322
DOI: 10.1056/NEJM199505183322001

Lower annual rates of VOC

Longer median time to first VOC

Decreased rates of ACS & transfusions

Hydroxyurea

Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG)

Prof Winfred C Wang, MD • Prof Russell E Ware, MD • Prof Scott T Miller, MD • Prof Rathi V Iyer, MD • Prof James F Casella, MD • Caterina P Minniti, MD • Prof Sohail Rana, MD • Courtney D Thornburg, MD • Prof Zora R Rogers, MD • Ram V Kalpatthi, MD • Prof Julio C Barredo, MD • R Clark Brown, MD • Prof Sharada A Sarnaik, MD • Prof Thomas H Howard, MD • Lynn W Wynn, MSN • Prof Abdullah Kutlar, MD • Prof F Daniel Armstrong, PhD • Beatrice A Files, MD • Jonathan C Goldsmith, MD • Myron A Waclawiw, PhD • Xiangke Huang, MD • Bruce W Thompson, PhD for the BABY HUG investigators • Show less

THE LANCET

ARTICLES | VOLUME 377, ISSUE 9778, P1663-1672, MAY 14, 2011

↓ Decreased incidence of pain/dactylitis

↑ Increased Hb and HbF

↓ Decreased WBC

Hydroxyurea

- Overall association with:
  - Lower rates of VOC
  - Lower rates of ACS
  - Decreased transfusion requirements
  - Increased total hemoglobin/HbF
  - Lower hospitalization costs for VOC

Exhibit 12. Evidence Profile—Evidence of Efficacy/Effectiveness for Children and Adults With Sickle Cell Anemia (Hydroxyurea Versus Usual Care)

Outcome	Quality of the Evidence	Treatment Effect
Pain crises	High	Statistically significant benefit
Acute chest syndrome	Moderate	Statistically significant benefit
Hemoglobin level, fetal hemoglobin level, need for blood transfusions	Moderate	Statistically significant benefit
Mortality	Low	Imprecise estimate
Stroke	Low	Imprecise estimate

NHLBI Guidelines 2014; Multicenter Study of Hydroxyurea in Patients with Sickle Cell Anemia 1994

Hydroxyurea

Recommended initiation criteria (NHLBI)

- Adults
  - ≥ 3 moderate-severe vaso-occlusive episodes in 12 months or pain interfering with ADL/QOL
  - History of severe/recurrent ACS
  - Symptomatic, chronic anemia interfering with ADL/QOL
- Children
  - HbSS or HbSβ^0 thalassemia, ≥ 9 months of age regardless of clinical severity

Hydroxyurea

- Pre-initiation labs
  - CBC/differential, reticulocyte count, HbF, CMP, pregnancy test
- Starting dose
  - Adults: 15 mg/kg/day
  - Children: 20 mg/kg/day
  - Escalate dose by 5 mg/kg until 35 mg/kg/day or persistent myelosuppression
- Monitor for cytopenias
  - Thrombocytopenia (goal $\geq$ 80,000)
  - Neutropenia (goal $\geq$ 1250-2000)

Exhibit 13. Evidence Profile—Evidence of Side Effects in Sickle Cell Anemia

Potential Toxicity	Quality of the Evidence	Treatment Effect
Bone marrow suppression	High	Reversible cytopenias associated with hydroxyurea
Leukemia	No supporting evidence in SCD populations/Very low	The available evidence does not support the association of hydroxyurea treatment with the development of leukemia in adults or children
Leg ulcers	Adults: Moderate Children: Low	The available evidence does not support the association of hydroxyurea treatment with leg ulcers
Other side effects	Very low	Numerous other side effects were reported in the literature with low frequency and none with certain causality
Reproductive effects	Very low	Minimal human data exist on potential harmful reproductive effects of hydroxyurea in males and females

NHLBI 2014 Guidelines

Case Study 2

- A 5 year old female with Hemoglobin SS has had increasing intracranial velocities on transcranial doppler screenings (TCDs) over the past 2 years. Her TCD performed today has a left MCA1 velocity of 202 cm/sec. What intervention is indicated for her at this time?

Chronic Transfusions

- Indicated for primary and secondary stroke prevention

Exhibit 18. Chronic Complications—Graded Recommendations for When To Initiate a Chronic Transfusion Program

Indication	How To Transfuse	Quality of Evidence	Strength of Recommendation
Child with transcranial Doppler (TCD) reading* >200 cm/sec	Exchange or simple transfusion	High	Strong
Adults and children with previous clinically overt stroke	Exchange or simple transfusion	Low	Moderate

NHLBI 2014 Guidelines

Chronic Transfusions

- NHLBI/ASH
  - Usual goal of ≤ 30% HbS (STOP 1/STOP 2 protocols)
  - Initiation: RBC phenotyping, T&S, %HbA, %HbS, CBC, reticulocyte count
  - Monitoring: CBC, reticulocyte count, %HbA, %HbS, T&S, LFTs, ferritin, viral screenings
  - MRI screening for liver iron content (LIC) every 1-2 years.
    - Most useful if ferritin is >1000 and/or patient is not receiving red cell exchange transfusions.
  - Units should be leukoreduced, sickle negative, minor antigen matched

Chronic Transfusions

- ASH recommendations:
  - Extended RBC antigen typing
    - Minimum requirements: C/c, E/e, K, Jk^a/Jk^b, Fy^a/Fy^b, M/N, and S/s
  - Suggests automated RCE > simple transfusion or manual RCE in all SCD genotypes receiving chronic RBC transfusions

Chronic Transfusions

- Complications
  - Alloimmunization/autoimmunization
  - Iron overload
  - Delayed hemolytic transfusion reaction
  - Hyperviscosity

Case Study 3

- A 3 year old male with Hemoglobin SS and no significant complications to date presents to your clinic for a routine visit. His parents are interested in discussing curative options. Which curative option carries with it the highest rate of success and lowest rate of complications/rejection?

Hematopoietic Stem Cell Transplant

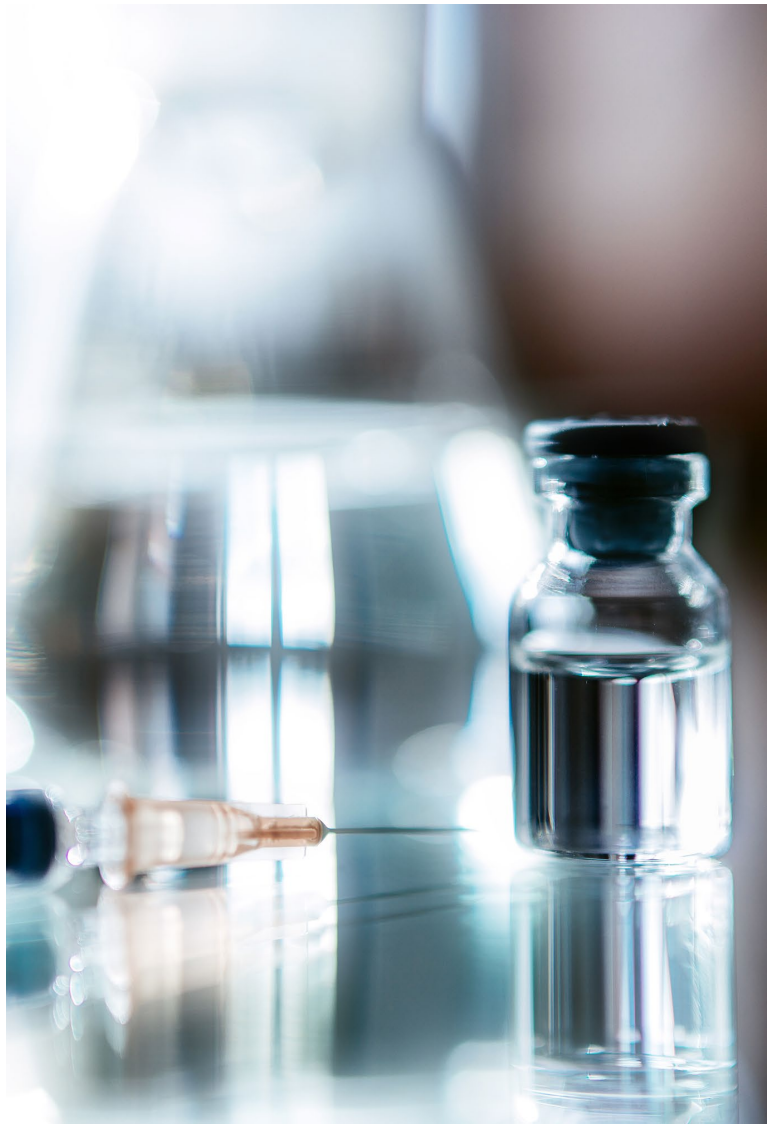
- HSCT in sickle cell disease
  - Allogenic
    - Matched related donor
    - Matched unrelated donor
    - Haploidentical donor
  - Conditioning regimens
    - Myeloablative
    - Nonmyeloablative
    - Reduced intensity
  - Marrow preferred over cord blood
    - Reduced quantity of T cells
    - Lower risk of GVHD

Hematopoietic Stem Cell Transplant

- Considerations
  - SCD-related complications to date
  - Anticipated morbidity/mortality risks of HSCT
    - EFS 93% for <16 years, 81% for ≥ 16 years
  - Age of patient
    - 5 year OS when transplanted <16 years – 95%
    - 5 year OS when transplanted ≥ 16 years – 81%
  - Donor availability
  - Clinical trial eligibility

Hematopoietic Stem Cell Transplant

- Preparation
  - HLA typing of patient and potential donor(s)
  - Conditioning regimen for recipient bone marrow ablation
  - GVHD/infection prophylaxis
- Typical course of treatment
  - Transfusion support as needed during engraftment
  - Immunosuppressive therapy (gradual wean)
  - Long term follow up



Hematopoietic Stem Cell Transplant

- Risks
  - Gonadal dysfunction
  - GVHD
  - Malignancy
    - May be higher in transplant approaches resulting in mixed chimerism

Case Study 4

- A 14 year old female with Hemoglobin SC presents to your hematology clinic for a semiannual visit. She has had 5 vaso-occlusive pain episodes within the past year, including 1 which resulted in hospital admission. She has difficulty with venous access attempts and has no conveniently-located lab facilities nearby. Her parents request additional information regarding disease-modifying therapies. Of the oral medications available, which do you prioritize for discussion?

L-Glutamine

An amino acid used in nicotinamide adenine dinucleotide (NAD) synthesis.

NAD/NADH help to prevent oxidative damage to RBCs.

Sickled RBCs have a decreased redox ratio and increased uptake of L-glutamine as compared to normal RBCs.

L-glutamine is thought to decrease oxidative stress and decrease endothelial adhesion of sickled RBCs.

L-Glutamine

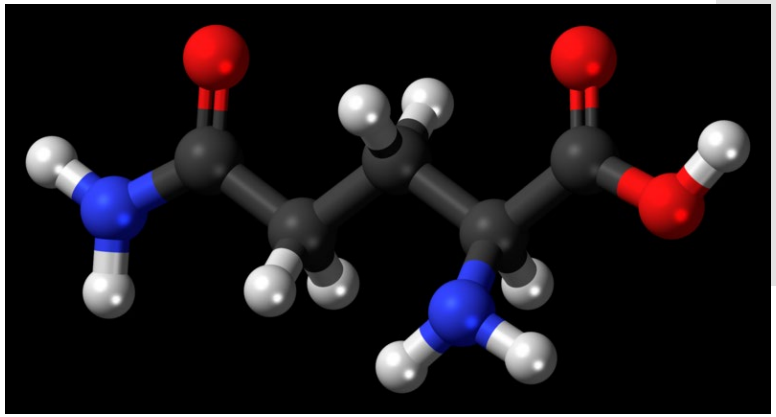
ORIGINAL ARTICLE

A Phase 3 Trial of L-Glutamine in Sickle Cell Disease

Yutaka Niihara, M.D., M.P.H., Scott T. Miller, M.D., Julie Kanter, M.D., Sophie Lanzkron, M.D., M.H.S., Wally R. Smith, M.D., Lewis L. Hsu, M.D., Ph.D., Victor R. Gordeuk, M.D., Kusum Viswanathan, M.D., Sharada Sarnaik, M.D., Ifeyinwa Osunkwo, M.D., Edouard Guillaume, M.D., Swayam Sadanandan, M.D., Lance Sieger, M.D., Joseph L. Lasky, M.D., Eduard H. Panosyan, M.D., Osbourne A. Blake, M.D., Tamara N. New, M.D., Rita Bellevue, M.D., Lan T. Tran, M.P.H., Rafael L. Razon, M.D., Charles W. Stark, Pharm.D., Lynne D. Neumayr, M.D., and Elliott P. Vichinsky, M.D. for the Investigators of the Phase 3 Trial of L-Glutamine in Sickle Cell Disease*

July 19, 2018
N Engl J Med 2018; 379:226-235
DOI: 10.1056/NEJMoa1715971

- 230 patients
  - 5-58 years
  - 53.9% female
  - 152 received L-glutamine, 78 received placebo
- Decreased median number of VOC events irrespective of concurrent hydroxyurea use
  - Median of 3 total over 48 weeks vs. 4 total in placebo group
- Decreased number of hospital admissions
  - Median of 2 vs. 3 in placebo group



L-Glutamine

Dissolvable powder, weight-based dosing		
<30 kg: 5 g BID	30-65 kg: 10 g BID	> 65 kg: 15 g BID

Mix into 8 oz of beverage or 4-6 oz of food.

- No known contraindications.
  - Use with caution in patients with hepatic or renal impairment.
- Most common side effects are gastrointestinal: flatulence, constipation, nausea
  - Less common: headache, cough, chest pain, musculoskeletal pain
- No required laboratory monitoring
- Oral administration
- May be used concurrently with hydroxyurea

Case Study 5

- A 12 year old male with Hemoglobin SS presents to your hematology clinic for a quarterly visit. His hemoglobin has been persistently low (7-8 g/dL range) with increased markers of hemolysis despite reported adherence to hydroxyurea at MTD. You would like to offer the family an additional option for management of his sickle cell disease. Which medication do you suggest?

Voxelotor

HbS polymerization inhibitor

Increases oxygen affinity of hemoglobin

Decreases indirect bilirubin and reticulocyte % (markers of hemolysis)

Voxelotor

ORIGINAL ARTICLE

A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease

Elliott Vichinsky, M.D., Carolyn C. Hoppe, M.D., Kenneth I. Ataga, M.D., Russell E. Ware, M.D., Ph.D., Videlis Nduba, M.B., Ch.B., M.P.H., Amal El-Beshlawy, M.D., Hoda Hassab, M.D., Maureen M. Achebe, M.D., M.P.H., Salam Alkindi, M.B., B.Ch., R. Clark Brown, M.D., Ph.D., David L. Diuguid, M.D., Paul Telfer, M.D., Dimitris A. Tsitsikas, M.D., Ashraf Elghandour, M.D., Victor R. Gordeuk, M.D., Julie Kanter, M.D., Miguel R. Abboud, M.D., Joshua Lehrer-Graiwer, M.D., Margaret Tonda, Pharm.D., Allison Intondi, Ph.D., Barbara Tong, Ph.D., and Jo Howard, M.D. for the HOPE Trial Investigators*

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Voxelotor, 1500 mg (N=90)	Voxelotor, 900 mg (N=92)	Placebo (N=92)
Age — yr			
Median	24	24	28
Range	12–59	12–59	12–64
Age group — no. (%)			
12 to <18 yr	14 (16)	15 (16)	17 (18)
≥18 yr	76 (84)	77 (84)	75 (82)
Female sex — no. (%)	58 (64)	51 (55)	50 (54)
Race or ethnic group — no. (%)†			
Black	59 (66)	61 (66)	63 (68)
Arab or Middle Eastern	20 (22)	20 (22)	20 (22)
White	12 (13)	7 (8)	5 (5)
Asian	1 (1)	1 (1)	0
Other	2 (2)	5 (5)	6 (7)
Geographic region — no. (%)			
North America	34 (38)	36 (39)	35 (38)
Europe	19 (21)	19 (21)	18 (20)
Other	37 (41)	37 (40)	39 (42)
Sickle cell disease genotype — no. (%)			
Homozygous hemoglobin S	61 (68)	71 (77)	74 (80)
Hemoglobin Sβ^0-thalassemia	18 (20)	13 (14)	11 (12)
Hemoglobin Sβ^+-thalassemia	7 (8)	2 (2)	3 (3)
Hemoglobin SC	3 (3)	2 (2)	2 (2)
Other variant	1 (1)	4 (4)	2 (2)
Baseline hemoglobin level — g/dl			
Median	8.7	8.3	8.6
Range	5.9–10.8	5.9–10.8	6.1–10.5
No. of vaso-occlusive crises in the past 12 months — no. of patients (%)			
1	35 (39)	41 (45)	39 (42)
2–10	55 (61)	51 (55)	53 (58)
Patients receiving hydroxyurea at baseline — no. (%)	58 (64)	63 (68)	58 (63)

* There were no significant between-group differences in demographic and clinical characteristics at baseline. Percentages may not total 100 because of rounding.
† Race or ethnic group was self-reported; participants could be included in more than one category of race or ethnic group.

August 8, 2019
N Engl J Med 2019; 381:509-519
DOI: 10.1056/NEJMoa1903212

- ~66% of patients were taking hydroxyurea concurrently

Voxelotor

- HOPE study
  - Inclusion criteria: 1-10 VOE within 12 months, baseline Hb 5.5-10.5 g/dL.
  - Exclusion criteria: RBC transfusion $\leq$ 60 days, erythropoietin $\leq$ 28 days, renal insufficiency, uncontrolled liver disease, pregnancy, lactating.
  - Primary endpoint: percentage of participants with a hemoglobin increase of > 1 g/dL at week 24.

Voxelotor

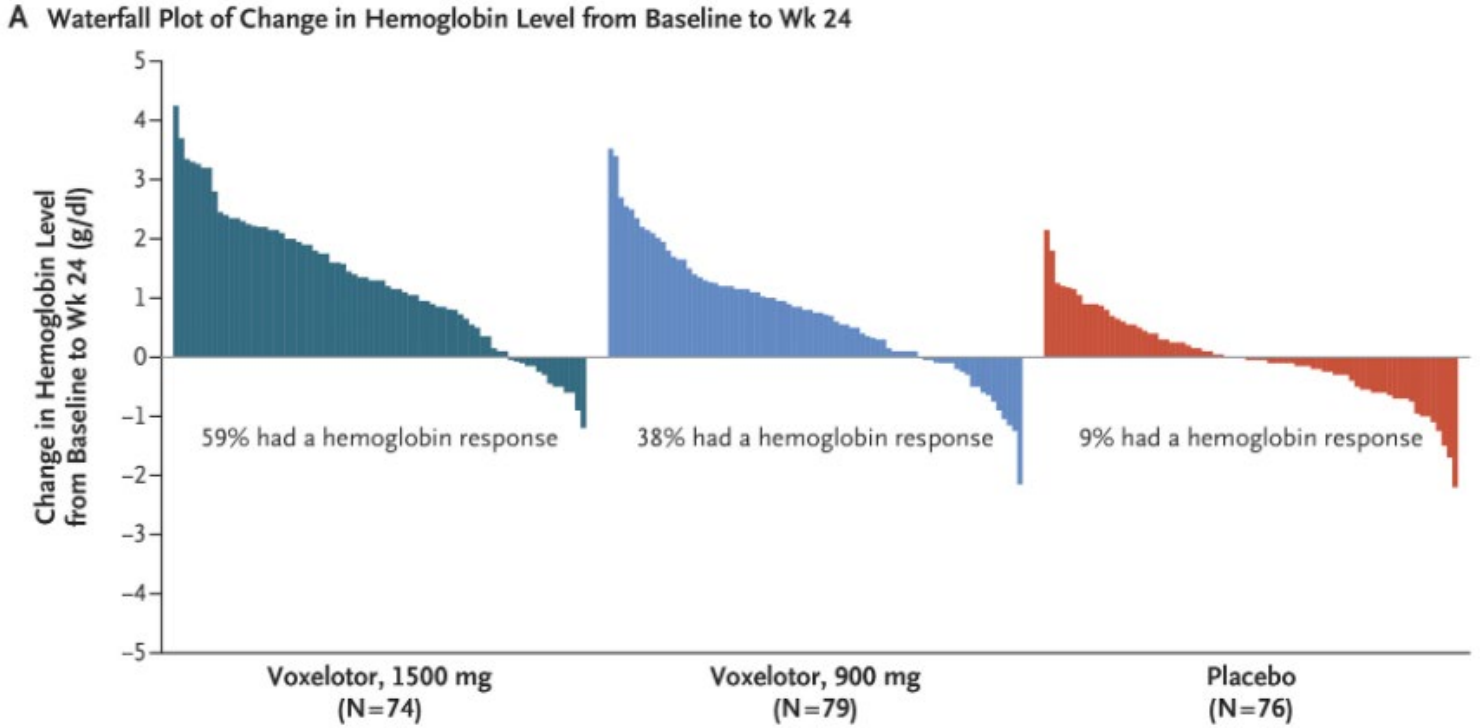


Table 2. Change in the Levels of Hemoglobin and Markers of Hemolysis from Baseline to Week 24.*

Variable	Voxelotor, 1500 mg		Voxelotor, 900 mg		Placebo	
	No. of Participants†	Change from Baseline to Week 24‡	No. of Participants†	Change from Baseline to Week 24‡	No. of Participants†	Change from Baseline to Week 24‡
		LS mean (95% CI)		*LS mean (95% CI)*		*LS mean (95% CI)*
Absolute change in hemoglobin level — g/dl	88	1.1 (0.9 to 1.4)§	92	0.6 (0.3 to 0.8)	91	−0.1 (−0.3 to 0.2)
Relative change in indirect bilirubin level — %	85	−29.1 (−35.9 to −22.2)§	88	−20.3 (−27.1 to −13.6)	85	−3.2 (−10.1 to 3.8)
Relative change in percentage of reticulocytes — %	88	−19.9 (−29.0 to −10.9)§	92	−1.3 (−10.3 to 7.7)	91	4.5 (−4.5 to 13.6)
Relative change in absolute reticulocyte count — %	88	−8.0 (−18.1 to 2.1)	92	5.1 (−4.9 to 15.2)	91	3.1 (−7.0 to 13.2)
Relative change in lactate dehydrogenase level — %	88	−4.5 (−11.9 to 2.8)	90	1.4 (−5.9 to 8.7)	87	3.4 (−4.0 to 10.9)

Voxelotor

Dosing

(Available in 300 mg and 500 mg tablets as well as 300 mg tablets for oral suspension)

> Age 12	Age 4-12, ≥ 40 kg	Age 4-12, 20-39.9 kg	Age 4-12, 10 kg-19.9 kg
1500 mg daily	1500 mg daily	900 mg	600 mg

- Contraindication:
  - Prior drug sensitivity
  - Use alternate dosing in patients with severe hepatic impairment
- Most common side effects are headache, diarrhea, abdominal pain, nausea, rash, and pyrexia
- Oral administration
- May be used concurrently with hydroxyurea

Case Study 5

- A32 year old female with Hemoglobin SS presents to your hematology clinic for a quarterly visit. Her interval history is notable for 3 VOEs, 1 of which resulted in a 7 day admission. She is adherent to hydroxyurea therapy, prescribed at MTD. What additional medication do you offer her to decrease the frequency of her VOEs?

Crizanlizumab

P-selectin monoclonal antibody

Binds to P-selectin on activated endothelium and platelets

Inhibits leukocyte, erythrocyte, platelet, and endothelial interactions.

Crizanlizumab

ORIGINAL ARTICLE

Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease

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Table 1. Characteristics and Baseline Values of the Patients in the Intention-to-Treat Population.*

Characteristic	High-Dose Crizanlizumab (N=67)	Low-Dose Crizanlizumab (N=66)	Placebo (N=65)
Age — yr			
Median	29	29	26
Range	16–63	17–57	16–56
Sex — no. (%)			
Male	32 (48)	30 (45)	27 (42)
Female	35 (52)	36 (55)	38 (58)
Race — no. (%)†			
Black	60 (90)	62 (94)	60 (92)
White	4 (6)	2 (3)	3 (5)
Other	3 (4)	2 (3)	2 (3)
Sickle cell disease genotype — no. (%)			
HbSS	47 (70)	47 (71)	47 (72)
Other‡	20 (30)	19 (29)	18 (28)
Concomitant hydroxyurea use — no. (%)			
Yes	42 (63)	41 (62)	40 (62)
No	25 (37)	25 (38)	25 (38)
Sickle cell–related pain crises during previous 12 mo — no. (%)			
2–4 crises	42 (63)	41 (62)	41 (63)
5–10 crises	25 (37)	25 (38)	24 (37)

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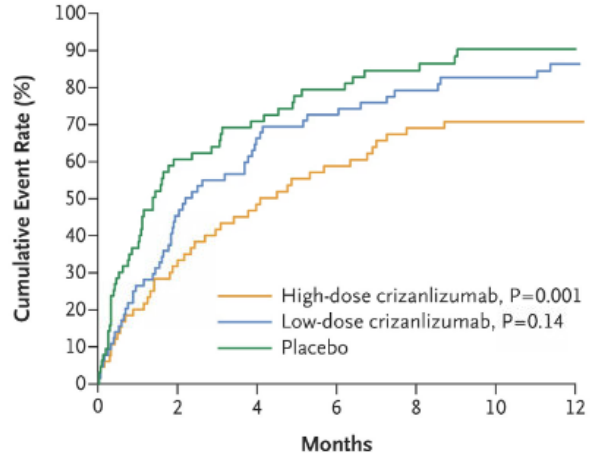
- ~62% of patients were taking hydroxyurea concurrently

Crizanlizumab

- SUSTAIN trial
  - Inclusion criteria: 16-65 years with SCD, male or female on birth control or of non-childbearing potential, dose-stabilized on hydroxyurea or erythropoietin, 2-10 VOE within the previous 12 months.
  - Exclusion criteria: chronic or exchange transfusions, Hb < 4 g/dL, planned surgical procedure, plans for modification of HU, chronic anticoagulation, active/unstable cardiac, neurologic, endocrine, hepatic, or renal dysfunction, h/o malignancy within 5 years, h/o stroke within 2 years, HIV, +UDS, significant mental or physical illness which could lead to impairment
  - Primary endpoint: annual rate of SCD-related VOE

Crizanlizumab

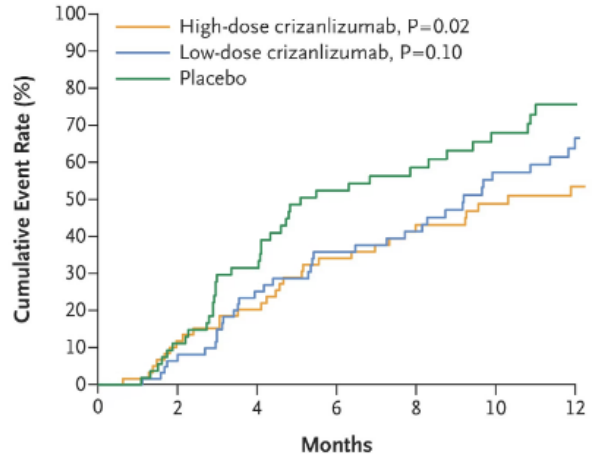
A First Sickle Cell–Related Pain Crisis



No. at Risk

High-dose crizanlizumab	67	49	41	35	30	26	24	20	18	17	16	15	7
Low-dose crizanlizumab	66	47	34	28	21	19	17	15	12	10	10	10	3
Placebo	65	37	23	21	17	13	12	9	8	6	5	4	1

B Second Sickle Cell–Related Pain Crisis



No. at Risk

High-dose crizanlizumab	67	60	52	50	46	41	38	35	31	30	26	22	9
Low-dose crizanlizumab	66	62	56	50	43	40	36	34	31	26	21	20	7
Placebo	65	55	48	38	36	27	25	22	18	16	13	10	3

Table 2. Annual Rates of Sickle Cell–Related Pain Crises.*

Variable	High-Dose Crizanlizumab	Low-Dose Crizanlizumab	Placebo
Primary end point: annual rate of crises in the intention-to-treat population			
No. of patients	67	66	65
Median rate of crises per year (IQR)	1.63 (0.00–3.97)	2.01 (1.00–3.98)	2.98 (1.25–5.87)
Difference from placebo — %	–45.3	–32.6	—
P value	0.01	0.18	—
No. of patients with crisis rate of zero at end of trial	24	12	11
Annual rate of crises in the per-protocol population			
No. of patients	40	44	41
Median rate of crises per year (IQR)	1.04 (0.00–3.42)	2.00 (1.00–3.02)	2.18 (1.96–4.96)
Difference from placebo — %	–52.3	–8.3	—
P value	0.02	0.13	—
No. of patients with crisis rate of zero at end of trial	15	7	5
Subgroup analyses in the intention-to-treat population			
According to concomitant hydroxyurea use			
Use			
No. of patients	42	41	40
Median rate of crises per year (IQR)	2.43 (0.00–4.01)	2.00 (1.00–3.93)	3.58 (1.13–6.23)
Difference from placebo — %	–32.1	–44.1	
No use			
No. of patients	25	25	25
Median rate of crises per year (IQR)	1.00 (0.00–2.00)	2.16 (1.89–3.98)	2.00 (1.63–3.90)
Difference from placebo — %	–50.0	8.0	—
According to no. of crises in previous 12 mo			
2–4 crises			
No. of patients	42	41	41
Median rate of crises per year (IQR)	1.14 (0.00–3.96)	2.00 (1.00–3.02)	2.00 (1.00–3.90)
Difference from placebo — %	–43.0	0.0	—
5–10 crises			
No. of patients	25	25	24
Median rate of crises per year (IQR)	1.97 (0.00–3.98)	3.02 (2.00–5.19)	5.32 (2.01–11.05)
Difference from placebo — %	–63.0	–43.2	—
According to sickle cell disease genotype			
HbSS			
No. of patients	47	47	47
Median rate of crises per year (IQR)	1.97 (0.00–3.96)	2.05 (1.00–4.96)	3.01 (1.01–6.00)
Difference from placebo — %	–34.6	–31.9	—
Other			
No. of patients	20	19	18
Median rate of crises per year (IQR)	0.99 (0.00–4.01)	2.00 (1.00–3.03)	2.00 (1.86–5.00)
Difference from placebo — %	–50.5	0.0	—

* The primary end point was the annual rate of crises in the high-dose crizanlizumab group versus the placebo group. The intention-to-treat population included all patients who underwent randomization. The per-protocol population included all the patients who underwent randomization, received at least 12 of the 14 planned doses of crizanlizumab or placebo, and had no major protocol violations that would affect the efficacy assessments. P values are for the comparison between the active-treatment group and placebo and were calculated with the use of a stratified Wilcoxon rank-sum test. IQR denotes interquartile range.

Crizanlizumab

Administration

5 mg/kg by IV infusion over 30 minutes

Week 0 and Week 2 followed by every 4 weeks following

- Contraindications: None
- Most common side effects are nausea, arthralgia, back pain, abdominal pain, and pyrexia
- IV administration
- May be used concurrently with hydroxyurea

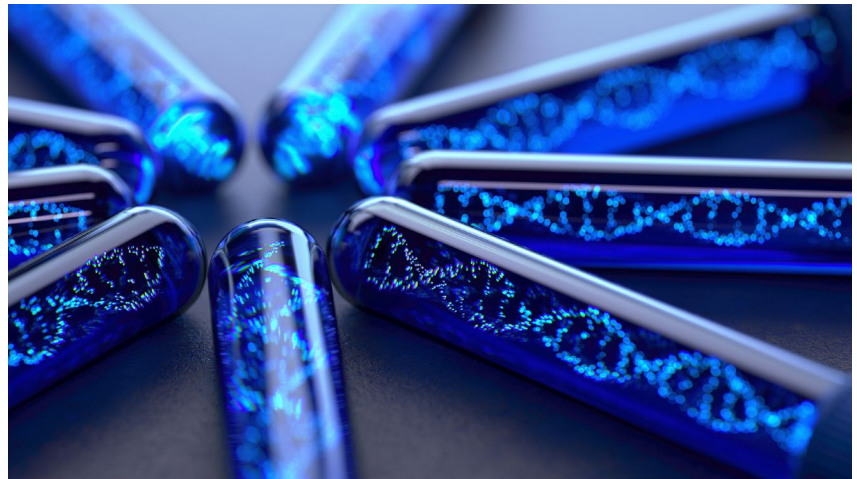
Case Study 6

- A26 year old male with Hemoglobin Sβ^0 thalassemia presents to your hematology clinic for a new patient visit. His SCD has been relatively well-controlled to date, with no history of ACS, cardiac dysfunction, hepatic dysfunction, or renal dysfunction and fewer than 5 lifetime blood transfusions. He has been adherent to hydroxyurea at an MTD of 35 mg/kg for many years. He is an only child. Today, he is interested in learning more about curative therapies for sickle cell disease. Other than HSCT, what emerging option do you discuss with him?

Gene Therapy

Replacement of HbS with nonsickling hemoglobin

- Gene addition
  - Viral vector used to introduce a nonsickling globin gene
    - Both HbS and new Hb are subsequently produced.
- Gene editing
  - Enzyme used to target DNA to modify sequences leading to HbF production and HbS suppression
- Gene silencing
  - Viral vector interferes with messenger RNA to block a HbF-suppressing transcription factor
- Gene correction
  - Guide RNA removes a target mutation and delivers a template DNA sequence.

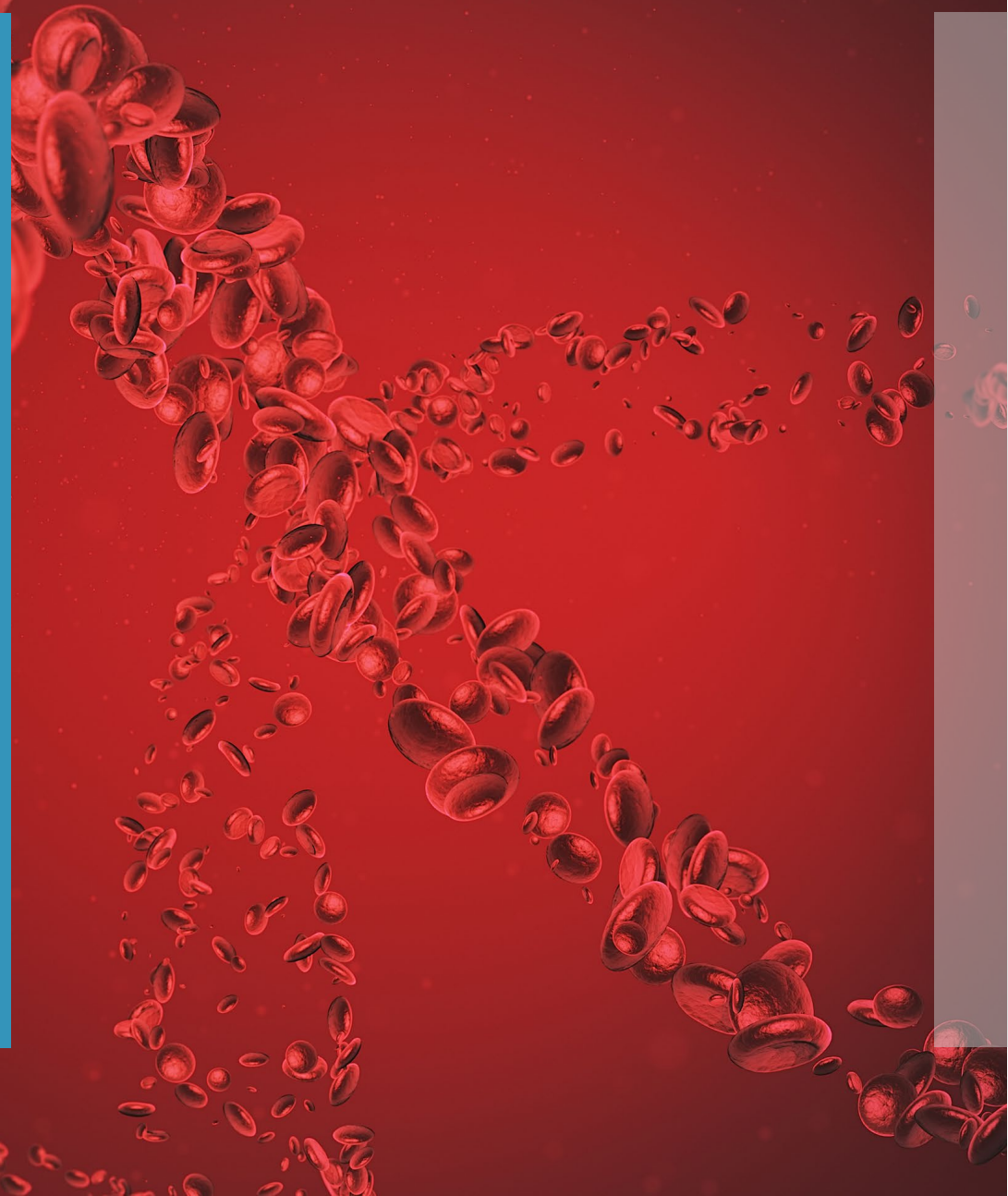


Gene Therapy

- SCD is suitable for gene therapy research due to its single point mutation origin.
- Currently only available in the context of clinical trials
- Risks include infertility and additional side effects from conditioning regimen as well as secondary malignancy due to chemotherapy, transplantation of damaged stem cells, or gene insertion at a promoter site.

Conclusions

- Treatment options for people with sickle cell disease have expanded in recent years
- Discussions regarding options can be tailored to each person's individual needs and desires
- Becoming familiar with availability of treatment options will help to expand access to disease-modifying therapies for people with sickle cell disease.



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Questions?

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