Sickle Cell Disease: Past, Present, & Future

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Disclosures

► None
Objectives

- Brief overview of sickle cell disease
  - Historical perspective
  - Pathophysiology and common complications
- Review current state of SCD and standard(s) of care
  - Treatment strategies and current guidelines
- Discuss future directions in treatment of SCD
  - Emerging therapies and clinical trials

Sickle Gene Areas of Origin
Hemoglobin S and Malaria
Sickle Cell Disease in Africa

- As many as 20-30% of the population in certain parts of Africa carry the gene for SCD
- As many as 150,000 children are born in Africa each year with sickle cell disease
- Majority die before 5 years of age from infectious complications
- Having sickle cell trait (SCT) confers at least partial resistance to malarial infection

SCD in North America

- Dr. James Herrick – 1904
- Dental student from Grenada presented to Chicago hospital with muscle pain, headaches, heart palpitations
- Unusual findings on blood smear
Blood Sample from Walter Noel

"Peculiar, elongated and sickle-shaped red blood corpuscles"

12/31/1904

SCD in North America

- 1949 → Linus Pauling concludes SCD is due to defect in hemoglobin molecule
- 1956 → Hemoglobin S recognized as variant of Hemoglobin A with single amino acid substitution (valine for glutamate)
- 1960 → Structure of human hemoglobin identified
- 1972 → Nixon signs Sickle Cell Anemia Control Act into law
- 2006 → WHO recognized SCD as public health problem
SCD Treatment Milestones

- 1982 → First known cure of SCD with bone marrow transplantation
- 1986 → PCN prophylaxis shown to greatly reduce incidence of Pneumococcal infections in children with SCD
- 1995 → Hydroxyurea (HU) shown to reduce frequency of painful crises in adults with SCD
- 2006 → Newborn screening for SCD becomes universal in United States (recommended in 1987)
Sickle Cell Disease - Overview

- Inherited life-threatening disorder of red blood cells
- Affects 1 in 400 African American children born each year in U.S.
- ~100,000 people currently living with SCD in U.S.
- Caused by single β-globin gene mutation
  - Valine for glutamate at position 6
- Deoxygenation leads to formation of sickle-shaped RBC’s
  - HbSS, HbSC, HbSB⁺, HbSB⁰

Painful episodes are hallmark of disease
- Chronic pain becomes more prevalent throughout life
- More frequent VOE associated with early mortality
- Hospitalizations associated with decreased HRQOL
- Adolescents with SCD prone to social isolation, depression, anxiety
- SCD treatments have improved, however significant morbidity remains
Pathophysiology of SCD

- Complex process involving:
  - Microvascular occlusion
  - Endothelial damage
  - Oxidative stress
  - Cell adhesion
  - Inflammatory mediators

Sickle Cell Disease - Complications

- Acute painful episodes
- Hemolytic anemia
- Stroke
- Acute chest syndrome
- Fever/Infection
- Splenic sequestration
- Osteonecrosis
- Leg ulcers
- Priapism
- Pulmonary Hypertension
- Nephropathy
Acute Painful Episodes

- VOC/VOE → Hallmark complication of SCD
- Complicated and poorly understood process
  - Microvascular occlusion → Tissue ischemia → Tissue damage → Pain perception
- May be precipitated by exposure to cold, stress, infection, dehydration
- Can be result of “rebound” from incomplete resolution of previous pain episode
- Often can be treated at home with oral pain medications
- Goal is to minimize pain and prevent complications

Acute Painful Episodes: Management

- Parenteral analgesics
  - Morphine → at least 0.1 mg/kg, titrate to effect
  - Early initiation of patient-controlled analgesia (PCA)
  - Ketorolac → 0.5 – 1 mg/kg every 6 hours
  - Ask patient what works for them!
  - PRN = “patient receives nothing!”
- IV fluids ~ 1-1.25 x maintenance rate
- Labs → CBC with retic, culture if febrile, CXR if symptoms
Acute Painful Episodes: Management

- Consideration of RBC transfusion
- Supportive/alternative therapies
  - Massage, yoga, acupuncture, guided imagery, PT
- Bowel regimen
- Incentive spirometry
- Frequent reassessment of pain
- Transition to oral regimen when appropriate

Sickle Cell Disease: Current Preventative Treatment Strategies
Penicillin Prophylaxis

215 children with SCD under < 3 years of age at study entry

Randomized to Pen VK 125 mg BID vs placebo

Primary endpoint S. pneumo bacteremia

84% reduction in episodes of bacteremia in PCN group led to early study termination (13 in placebo vs 2 in PCN)

PCN prophylaxis now considered standard of care for children with SCD
Hydroxyurea

299 adults with SCD who experienced at least 3 pain crises in previous year
- 152 received HU (starting dose 15 mg/kg/day) vs 147 given placebo
- HU group showed:
  - Fewer crises during study period (2.5 vs 4.5 crises/year)
  - Longer time to first and second crises
  - Fewer episodes of ACS
  - Fewer transfusions
- No significant toxicities reported
Hydroxyurea

193 children 9 – 18 months of age at study entry
96 received HU at starting dose of 20 mg/kg/day
HU group showed:
- Fewer pain events including dactylitis
- Fewer episodes of ACS, hospitalization, transfusion
- Higher hemoglobin
- Higher fetal hemoglobin
- Led to recommendation of HU for children with SCD starting at 9 months of age
Red Cell Transfusion

- 130 children with SCD and TCD velocities of 200 cm/s or greater
- 63 randomized to transfusion protocol, 67 to “standard care”
- Primary endpoint was stroke incidence
- 10 strokes + 1 bleed in standard group vs 1 stroke in transfusion group
- 92% reduction in stroke incidence with transfusion protocol
121 patients (age 4–16) with SCD and abnormal TCD (> 200 cm/s) who had received at least 12 months of transfusion therapy

61 continued transfusions, 60 began Hydroxyurea therapy

No new strokes identified in either group during study period

Conclusion: patients with SCD and abnormal TCD without history of stroke can be safely transitioned to HU after receiving 1 year of transfusion therapy
Red Cell Transfusion

Stroke With Transfusions Changing to Hydroxyurea (SWiTCtCH)
Russell E. Ware1 and Ronald W. Helms,2 for the SWiTCtCH Investigators
1Baylor College of Medicine, Houston, TX; and 2Pho Inc, Chapel Hill, NC

Stroke is a devastating complication of sickle cell anemia (SCA) with high recurrence if untreated. Chronic transfusions reduce recurrent strokes but have associated morbidities including iron overload. Stroke With Transfusions Changing to Hydroxyurea (SWiTCtCH) was a multicenter phase 3 randomized trial comparing standard treatment (transfusions/chelation) to alternative treatment (hydroxyurea/pherlbotomy) for children with SCA, stroke, and iron overload. SWiTCtCH was a noninferiority trial with a composite primary end point, allowing an increased stroke risk but requiring superiority for removing iron. Subjects on standard treatment received monthly transfusions plus daily deferasirox iron chelation. Subjects on alternative treatment received hydroxyurea plus overlap transfusions during dose escalation to maximum tolerated dose (MTD), followed by monthly phlebotomy. Subjects on standard treatment (N=66) maintained 30% sickle hemoglobin (HbS) and tolerated deferasirox at 28.2 ± 6.0 mg/kg/d. Subjects on alternative treatment (N=67) initiated hydroxureas and 60 (90%) reached MTD at 26.2 ± 4.9 mg/kg/d with 29.1% ± 6.7% fetal hemoglobin (HbF). Adjudication documented no strokes on transfusions/chelation but 7 (10%) on hydroxyurea/pherlbotomy, still within the noninferiority stroke margin. The National Heart, Lung, and Blood Institute closed SWiTCtCH after interim analysis revealed equivalent liver iron content, indicating futility for the composite primary end point. Transfusions and chelation remain a better way to manage children with SCA, stroke, and iron overload. This clinical trial was registered at ClinicalTrials.gov NCT00122980. (Blood.2012;119(17):3925-3932)

133 children with SCD and history of documented stroke on transfusion protocol at least 18 months
66 continued transfusions, 67 transitioned to Hydroxyurea
No recurrent strokes in transfusion group, 7 in HU group
No differences in liver iron content
Conclusion: transfusion therapy remains best option for those who have had documented strokes
Other Health Maintenance

- Immunizations - standard childhood vaccines + PCV23
- Transcranial doppler screening
- Retinopathy screening
- Pre-operative transfusion to Hb > 10 g/dL
- Proteinuria screening
- Contraception/reproductive counseling
- Mental health screening
- AVN screening for those with persistent pain
- Cardiac screening for symptomatic patients

Published Guidelines for SCD

Special Communication
Management of Sickle Cell Disease
Summary of the 2014 Evidence-Based Report by Expert Panel Members

Barbara P. Yawn, MD, MSc, MSPH; George R. Buchanan, MD; Araba N. Afenya-Aman, MD, MPH; Samir K. Ballas, MD; Kathryn L. Hassell, MD; Andra H. James, MD, MPH; Lanetta Jordan, MD, MPH, MSPH; Sophie M. Langskron, MD, MHS; Richard Lottenberg, MD; William J. Savage, MD, PhD; Paula J. Tanabe, PhD, RN; Russell E. Ware, MD, PhD; M. Hassan Murad, MD, MPH; Jonathan C. Goldsmith, MD; Eduardo Ortiz, MD, MPH; Robinson Fulwood, PhD, MSPH; Ann Horton, MS; Joylene John-Sowah, MD, MPH
Emerging Therapies for Sickle Cell Disease

Strategic Targets

- Vasocclusion
- Inflammation
- HbS Polymerization
- Modifying the genotype
Strategic Targets

- Vasocclusion
- Inflammation
- HbS Polymerization
- Modifying the genotype

Glutamine

ORIGINAL ARTICLE

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


for the Investigators of the Phase 3 Trial of L-Glutamine in Sickle Cell Disease
Glutamine

- Glutamine thought to reduce oxidative stress in sickled erythrocytes by increasing reduced form of nicotinamide adenine dinucleotide (NADH)
- 230 patients (age 5 – 58 years) with HbSS or HbSB0 with 2 or more acute pain episodes in previous year
- Received L-glutamine (0.3 mg/kg/dose BID) vs placebo
- Primary endpoint was reduction in painful episodes
Glutamine

- Those in glutamine group experienced fewer pain episodes (3 vs 4) and hospitalizations (2 vs 3) during 48-week study period
- Also had longer time to first and second painful episodes
- Well-tolerated with generally non-specific side effects
- FDA approval of glutamine for SCD in those 5 years of age or older
- High cost, bad taste, poor compliance

Crizanlizumab

The NEW ENGLAND JOURNAL OF MEDICINE

Original Article

Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease

Crizanlizumab

- Monoclonal antibody against P-selectin
- Assigned to low dose, high dose, or placebo
- Administered IV 14 times over period of 52 weeks (+/- HU)
- Primary end point was annual rate of SCD-related pain crises
- 198 patients at 60 sites (ages 16 – 63)
- 63% decrease in pain crises in high dose treatment group
- Time to first crisis and hospital days also better in treatment group
- FDA approved in 2019 to reduce frequency of VOC in SCD patients 16 years and older

Strategic Targets

- Vasocclusion
- Inflammation
- HbS Polymerization
- Modifying the genotype
Targeting Inflammation in SCD

- **Statins**
  - Simvastatin found to reduce adhesion of white blood cells and when combined with HU decrease pain crises and markers of inflammation
- **N-Acetylcysteine (NAC)**
  - Shown to inhibit dense cell formation and restore glutathione levels toward normal; downward trend in decreased RBC sickling
- **Anticoagulant/Antiplatelet agents**
  - Rivaroxaban
  - Clopidogrel

Strategic Targets

- **Vasocclusion**
- **Inflammation**
- **HbS Polymerization**
- **Modifying the genotype**
Voxelotor

- Small molecule which acts to bind Hb S and stabilize in high oxygen affinity state, thereby inhibiting polymerization
- Reduces RBC sickling and decreased blood viscosity
- Results from Phase 2 studies showed ~ half of patients achieving increase in Hb of > 1 g/dL
- Improved indices of hemolysis, less pain, fewer transfusions
- FDA approved for SCD patients 12 and older in 2019; subsequently approved for ages 4 – 11 in 2022

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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., Amlal El-Beshlawy, M.D., Hoda Hassab, M.D., Maureen M. Achebe, M.D., M.P.H., Salim Alkandi, M.B., B.Ch., R. Clark Brown, M.D., Ph.D., David L. Diuguid, M.D., Paul Teller, M.D., Dimitris A. Tsitsikas, M.D., Ashraf Bighandour, M.D., Victor R. Gordon, M.D., Julie Kanter, M.D., Miguel R. Albredo, 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
Voxelotor

- 274 participants randomized to low-dose, high-dose, or placebo
- Once daily oral medication
- Primary end point was % of patients with hemoglobin response
- 51% in high-dose group had hemoglobin response
- Significant reductions from baseline in bilirubin and reticulocyte count
- Trend toward reduction in pain crises, though data still a bit unclear
- Similar results in pediatric trial leading to FDA approval

Strategic Targets

- Vasocclusion
- Inflammation
- HbS Polymerization
- Modifying the genotype
Bone Marrow Transplantation

- Only curative option for SCD currently
- Historically performed in patients with more severe disease course
  - History of stroke, recurrent ACS, > 3 pain crises/year
- Best results with matched sibling donors
  - Only 10 - 15% of patients have this option
- Historically relied on myeloablative conditioning regimens
  - Organ damage, infertility, secondary malignancies

Bone Marrow Transplantation

- Matched sibling transplants:
  - Largest series reported 93% EFS and 95% OS at 5 years
    - < 16 years = 95%, > 16 years = 81% OS
  - Low graft rejection, acceptable GVHD rates
  - Younger pts with fewer comorbidities fare better
- Matched unrelated donor transplants:
  - 69% EFS and 79% OS at 2 years
  - Chronic GVHD 62% at 1 year
  - 34% experienced PRES
Bone Marrow Transplantation

- Reduced intensity conditioning (RIC):
  - Allows for mixed chimerism and lower rates of GVHD
  - May ameliorate some toxicities of myeloablative conditioning
  - Higher rates of graft failure
- Haploidentical transplants:
  - Promising option to expand the donor pool in SCD
  - Current graft failure rates of 40 – 50%
  - Only in the context of clinical trials currently

Gene Therapy for SCD

Gene Therapy in a Patient with Sickle Cell Disease

Jean-Antoine Ribet, M.D., Ph.D., Salima Hacein-Bey-Abina, Pharm.D., Ph.D., Emmanuel Payen, Ph.D., Alessandra Maggini, M.D., Ph.D., Michaela Semerano, M.D., Ph.D., Elisa Magrin, Ph.D., Laure Caccavelli, Ph.D., Benedict Neven, M.D., Ph.D., Philippe Bourgey, Pharm.D., Ph.D., Wassim El Nemer, Ph.D., Pablo Bartolucci, M.D., Ph.D., Leslie Weber, M.Sc., Hervé Puy, M.D., Ph.D., Jean-François Meritet, Ph.D., David Crevent, M.D., Yves Beuzard, M.D., Stany Chrétien, Ph.D., Thibaud Lefèvre, M.D., Robert W. Ross, M.D., Olivier Negre, Ph.D., Gabor Veres, Ph.D., Laura Sandler, M.P.H., Sandeep Soni, M.D., Mariane de Montalembert, M.D., Ph.D., Stéphane Blanche, M.D., Philippe Leboulch, M.D., and Marina Cavazzana, M.D., Ph.D.
Gene Therapy for SCD

- Harvested bone marrow from patient
- Transduced CD-34+ cells with LentiGlobin BB305 vector
  - Lentivirus encodes for anti-sickling B-globin chain and production of modified adult hemoglobin (HbA T87Q)
- Myeloablative conditioning regimen with expected toxicities
- Autologous BMT
- Monitored for engraftment, HbA, HbS, HbF
Gene Therapy for SCD

Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease

Figure 32. LentiGlobin Treatment Process for KGR-206 Group C
(1) HSPC collection and enrichment
(2) LentiGlobin DP manufacturing
(3) Myeloablative conditioning using single-agent busulfan
(4) LentiGlobin DP infusion
(5) Engraftment of HSPCs and reparation
DP, drug product; HB, hemoglobin; HBA*α0,α0, HB with modified β-globin gene (β*α0,α0); RBS, sickle HB; HSPC, hematopoietic stem and progenitor cell; LAVV, lentiviral vector; RBC, red blood cell.
Gene Therapy for SCD

- Optimized treatment process when compared to earlier trials
  - Pre-transplant transfusion protocol
  - Cell mobilization with Plerixafor and collection via apheresis
  - Refined manufacturing process
- 35 patients received Lentiglobin infusion
- Increase in baseline hemoglobin from 8.5 g/dL to > 11 g/dL
- Reduction in markers of hemolysis
- Resolution of severe VOE
- 3+ years of follow up
Gene Therapy for SCD

Summary of Treatment Targets

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<th>Pathogenetic Mechanism</th>
<th>Counteragent</th>
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<td>P-selectin inhibition</td>
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<td>Polymerization</td>
<td>Voxelotor</td>
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<tr>
<td>Upregulation of fetal hemoglobin production</td>
<td>Hydroxyurea</td>
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<td>5-Azacytidine, Decitabine</td>
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<td>Oxidative stress</td>
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<tr>
<td>Genetic mutation</td>
<td>CRISPR/Cas 9 technology and transplantation</td>
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<tr>
<td>Abnormal rheology</td>
<td>Poloxamer 188</td>
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CRISPR/Cas 9, clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9.
References


Questions?

Thank you for your attention!