CENTENE PHARMACY
SERVICES

CENTENE® Corporation

Sickle Cell Anemia: Gene Editing

Hannah Hardy, Creighton University SPAHP PharmD Student

Lynneshia Bright, Florida A&M University COPPS PharmD Student

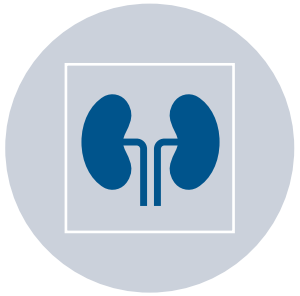
Quynh Nhu Nguyen, USF TCOP PharmD Student

Outline

- Background
- Epidemiology
- Pathophysiology
- Complications
- Non-pharmacological therapies
- Current pharmacological therapies
- New gene editing therapies

Background

Sickle cell disease (SCD) is an inherited disorder that affects hemoglobin: autosomal recessive



Serious health problems result from SCD: pain crisis, stroke, lung problems, infections, and kidney disease

Treatment reduces or helps manage symptoms

December 2023, the FDA approved 2 new gene therapies

Epidemiology – CDC

SICKLE CELL DISEASE WORLDWIDE

- Sickle cell disease affects millions of people throughout the world and is particularly common among those whose ancestors come from parts of the world where malaria is common:
  - Sub-Saharan Africa
  - Spanish-speaking regions in the Western Hemisphere (South America, the Caribbean, and Central America)
  - Saudi Arabia
  - India
  - Mediterranean countries such as Turkey, Greece, and Italy

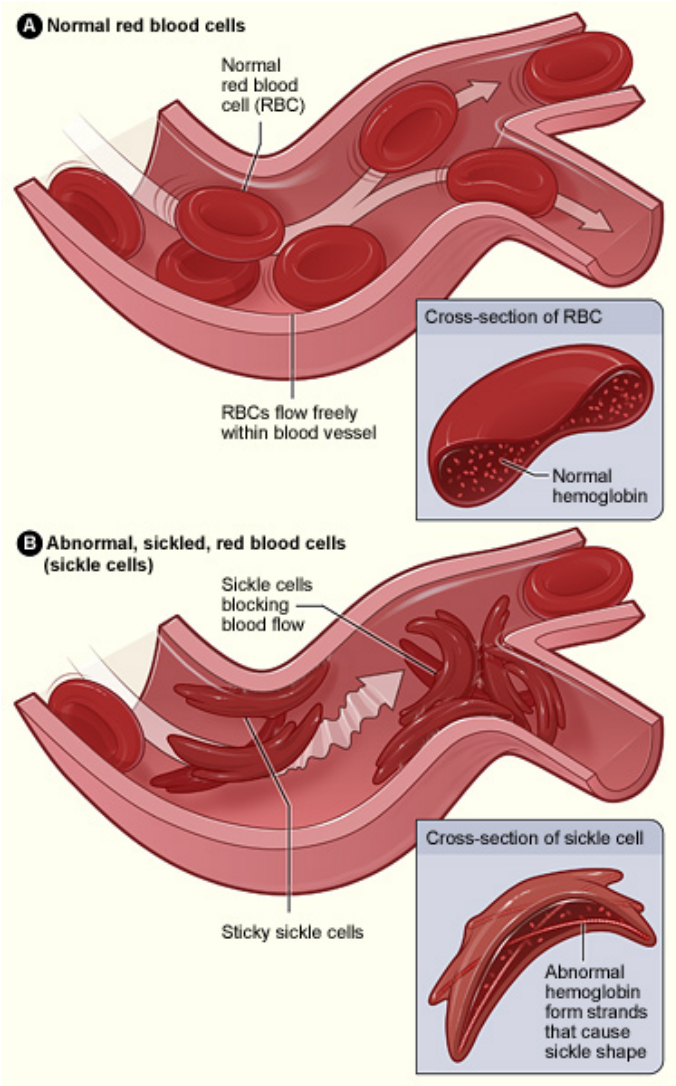
Epidemiology – CDC

SICKLE CELL DISEASE IN THE UNITED STATES

- Exact number of people living in the US with SCD is unknown, studies published in 2010 approximate 100,000
- More than 90% of people in the US with SCD are non-Hispanic Black or African American (Black), and an estimated 3 to 9% are Hispanic or Latino
- SCD occurs in about 1 out of every 365 Black or African American births and about 1 out of every 16,300 Hispanic American births
- About 1 in 13 Black or African American babies is born with sickle cell trait (SCT)

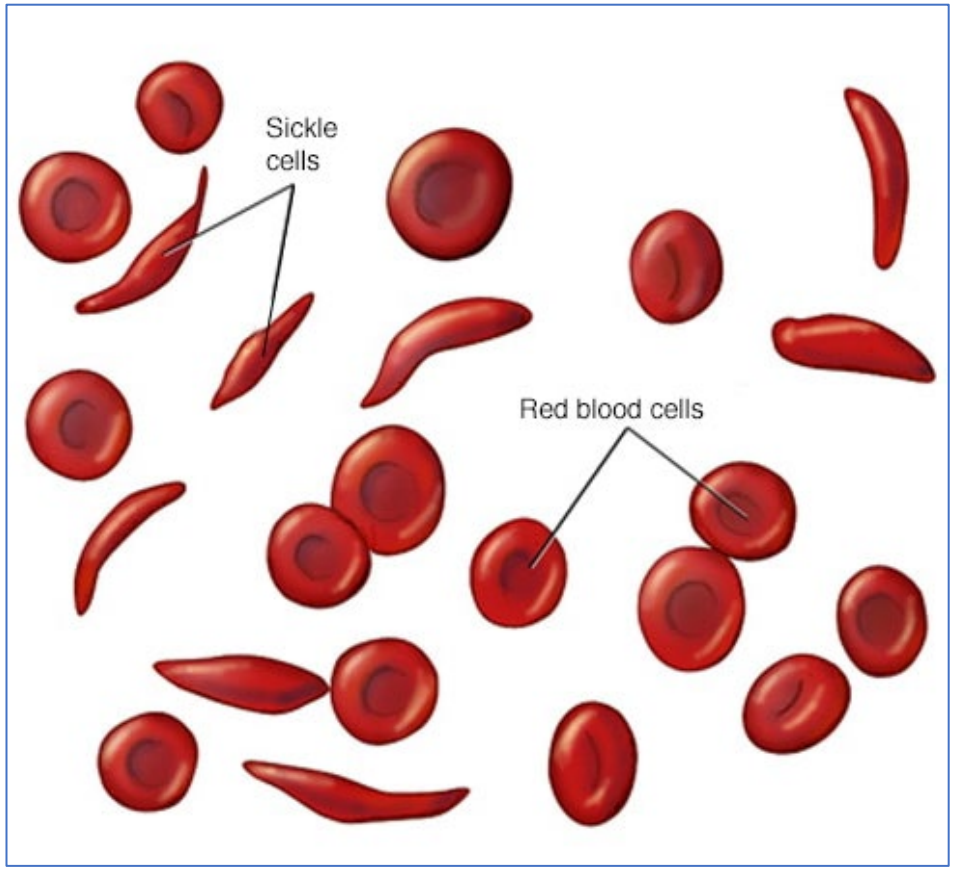
Pathophysiology

- Genetic mutations in the beta subunit of hemoglobin cause SCT and SCD
  - SCD is the result of "sickling" of red blood cells
  - SCD affects the rheologic properties of blood flow to all organs and throughout the body
  - Leads to:
    - Sickle cell anemia
    - Increase in blood viscosity and cell adhesion
    - Increase in acute and painful vaso-occlusion crisis (VOC)



Complications of Sickle Cell Disease

- Stroke
- Pain
- Acute Chest Syndrome
- Pulmonary hypertension
- Kidney disease
- Liver problems
- Splenic sequestration
- Blindness
- Sleep apnea
- Priapism
- Pregnancy complications



CENTENE PHARMACY SERVICES

Non-Pharmacological Treatment

CENTENE® Corporation

Non- Pharmacological Treatment

Transcutaneous electrical nerve stimulation

Yoga

Massage

Guided Audiovisual Relaxation

Cognitive Behavioral Therapy

Pharmacological Treatment

Classification of Pain

ACUTE PAIN

Vaso-occlusion of sickled red blood cells with ischemia reperfusion injury and tissue infarction

Presentation:

- One or multiple anatomic locations

CHRONIC PAIN

Sensitization of the central and/or peripheral nervous system

Presentation:

- Neuropathic pain
- Pain occurring over 6 months
- One or multiple anatomic locations

Acute Pain Management Treatment

Mild to Moderate

- Ibuprofen: 400-600 mg every 6 hours as needed
- Acetaminophen: 650- 1000 mg every 4-6 hours as needed
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

Severe Pain

- Morphine: 0.1-0.15mg/kg IV q 2-4 hours as needed
- Hydromorphone: 0.015-0.02 mg/kg IV q 3-4 hours as needed
- Opioid dosing based on consideration of baseline opioid therapy and prior effective therapy
- Conditional recommendation adults: moderate certainty in the evidence about effects ⊕⊕⊕◯
- Conditional recommendation children: low certainty in the evidence about effects ⊕⊕◯◯

Adjuvant Therapy

- Refractory: subanesthetic analgesic ketamine infusion 0.1- 0.3 mg/kg/hour every 4-6 hours as needed
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

Chronic Pain Management Treatment

Serotonin and Norepinephrine Reuptake Inhibitors

- Duloxetine: 30 mg by mouth once daily (max 120 mg/day)
- Milnacipran: 12.5 mg by mouth once daily (max 200mg/day)
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

Nonsteroidal Anti-inflammatory

- Ibuprofen: 400-600 mg every 6 hours as needed
- Acetaminophen: 650- 1000 mg every 4-6 hours as needed
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

Tricyclic Antidepressants

- Amitriptyline: 10-25 mg po once daily at bedtime (max 150 mg/day)
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

Chronic Pain Management Treatment Continued

Gabapentinoids

- Pregabalin: 75 mg by mouth twice daily
- Gabapentin: 300 mg once daily to three times a day
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

Severe Pain

- Morphine Extended release: 15 mg to 30 mg by mouth every 8 to 12 hours
- Methadone: 2.5 mg by mouth every 8 to 12 hours
- Used ONLY if refractory to multiple other interventions, chronic opioid therapy should be considered after risk stratification
- Conditional recommendation: very low certainty in the evidence about effects ⊕◯◯◯

Hydroxyurea (Xromi, Droxia, Siklos)

FDA Approved: Adults 1998 , Children 2017

Mainstay sickle cell management

- Mechanism of action
  - Target the ribonucleotide reductase enzymes, iron-containing enzymes that convert ribonucleoside diphosphates to deoxyribonucleotide triphosphates
- Dose
  - Children: 20 mg/kg/day by mouth once daily
  - Adults: 15 to 20 mg/kg/day by mouth once daily
  - CrCl <60 mL/min: 7.5 mg/kg/day by mouth once daily
  - Dose adjustments after 12 weeks by 2.5 mg/mL (max 35 mg/kg/day)
- Black Box Warnings
  - Bone marrow suppression, secondary malignancy
- Monitoring Parameters
  - Bone marrow suppression and CBC with Differential every 2 weeks
  - Avoid in Pregnancy
- Side Effects
  - Neutropenia, thrombocytopenia, nausea

Clinical Implication

- Reduction benefits
  - Frequency of Vaso-occlusive crisis in adults
    - p= < 0.001
  - Acute chest syndrome
    - Adults: p= < 0.01
    - Children: p= < 0.02
  - Hospitalizations
    - Children p= < 0.001
  - Stroke
    - p= 0.03
  - Transfusion
    - Adults: p= 0.001
    - Children: p= < 0.001

- Mortality:
  - Associated with a decreased mortality in symptomatic patients compared to patients without
    - 10- year survival improvement (86% compared to 65%, p= 0.001
  - Significantly reduced the median in both first and second pain crisis

L-Glutamine (Endari)

FDA Approved: 2017

- Mechanism of action
  - An amino acid that reduce SCD complication by decreasing oxidative stress
- Dose
  - <30 kg: Oral: 5 g twice daily (total dose 10 g/day)
  - 30 to 65 kg: Oral: 10 g twice daily (total dose 20 g/day)
  - >65 kg: Oral: 15 g twice daily (total dose 30 g/day)
- Side effect
  - Constipation, nausea, headache, abdominal pain, cough, pain in extremity, back pain, and chest pain
- Patient counseling
  - Mix with 8 oz of apple juice, water, or milk
  - Mix with 4-6 oz of yogurt or apple sauce

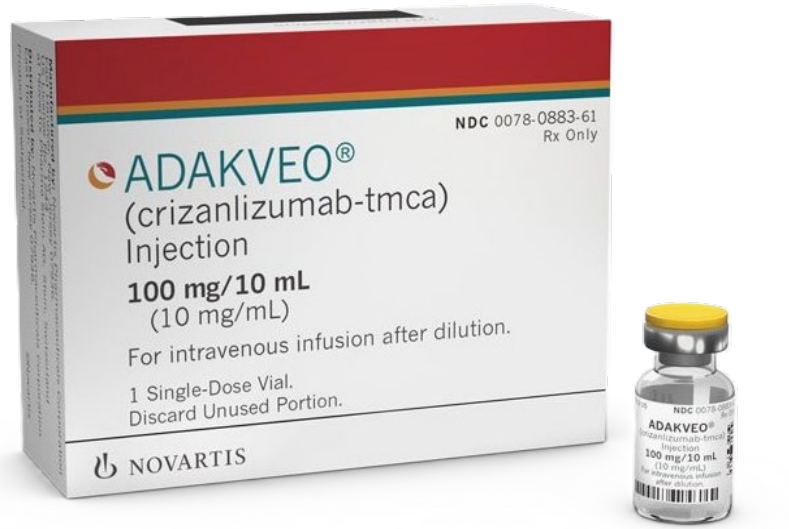
Clinical Implication

- Primary outcome
  - Significantly reduced annual rate of pain crises
    - 3.0 vs placebo 4.0, p=0.005
- Secondary Outcome
  - Longer median time to first crisis
    - 84 days vs placebo 54 days, p=0.02
  - Longer median time to second crisis
    - 212 days vs placebo 133 days, p=0.02
  - Reduced episodes of acute chest syndrome
    - 8.6% vs placebo 23.1%, p=0.003
  - Reduced rate of hospitalization
    - 2.0 vs placebo 3.0, p=0.005
- Efficacy
  - Reductions in the frequency of VOCs with hydroxyurea use
    - 36% of patients who received treatment compared to 17% of patients in placebo group did not experience a VOC
- Safety
  - L-glutamine showed lower adverse events compared to placebo

Crizanlizumab (Adakveo)

FDA Approved: 2019

- Mechanism of action
  - A humanized IgG2 kappa monoclonal antibody which binds to P-selectin and blocks interaction with ligands
- Dose
  - Adults : Injection 5 mg/kg IV once every 2 weeks for 2 doses (at week 0 and week 2), followed by 5 mg/kg IV once every 4 weeks
  - Can be used in combination with or without hydroxyurea
- Side effects
  - Infusion-related reaction, nausea, arthralgia, back pain, fever



Clinical Implication

- Primary outcome
  - Reduced annual rate of pain crises
    - 1.63 High-dose vs 2.98 placebo , 45.3% reduction , p= 0.01
- Secondary Outcome
  - Longer median time to first crisis
    - 4.07 vs. 1.38 months, p= 0.001
  - Longer median time to second crisis
    - 10.32 vs. 5.09 months, p= 0.02
  - Reduced rate of uncomplicated crises
    - 1.08 High-dose vs 2.91 placebo, 62.9% reduction , p= 0.02
- Efficacy
  - Reductions in the pain crises were observed with high-dose Crizanlizumab with or without hydroxyurea use
- Safety
  - Treatment showed similar incidence of adverse events compared to the placebo group

Disease Specific Treatment

Cardiopulmonary Disease

- Hydroxyurea
- Chronic red blood cell transfusion
- Asthma: Beta-adrenergic bronchodilators and oxygen prn

Stroke prevention in children with abnormal TCD

- Primary Stroke: chronic red blood cell transfusion
  - After 1 year transition to hydroxyurea
- Secondary and Acute Stroke: chronic red blood cell transfusion

Chronic Kidney Disease

- IV fluids
- Hydroxyurea
- ACE or ARB therapy

CENTENE PHARMACY SERVICES

Hematopoietic Stem Cells Transplantation (HSCT)

CENTENE® Corporation

Background Information

- Initially performed in 1984
- Mechanism
  - Healthy donor stem cells replace defective bone marrow cells. The transplanted cells will produce red blood cells with hemoglobin.
- Indications:
  - Severe SCD with complications of stroke, acute chest syndrome, recurrent pain crisis, nephropathy, retinopathy, osteonecrosis of multiple joints, and priapism
- Complications
  - Graft rejection, infection, chronic GVHD, and organ damage
- Cost: $87,000 -$300,000
- HLA Matching
  - HLA Class 1 (A, B, C) and Class II (DRB1, DQ)
  - 10/10 Match, 8/8 Match
  - Haploidentical Transplant
  - Cord Blood

Gene Therapy

Background Information

- Two available options:
  - Casgevy (exagamglogene autotemcel)
  - Lyfgenia (lovotibeglogene autotemcel)
- FDA Approval: December 8, 2023
  - For patients 12 years old and up
  - Indicated for patients with history of VOCs
- Cost: ~$2-3 million
- Duration of treatment: ~1 year

Comparison to Available Treatment

HEMATOPOIETIC STEM CELL TRANSPLANT

- Allogeneic
  - Requires a donor
    - Matched= limited availability
    - Haploidentical= only half matched
  - Risk of complications, including GVHD, rejection, and infections

GENE THERAPY

- Autologous
  - Utilizes patient's own stem cells
    - Avoids wait and search for potential donors
  - Avoids complications such as GVHD or rejection

Obstacles and Risks With Gene Therapy

- Availability of authorized treatment center (ATC)
  - Patient required to visit and be admitted at an ATC for various steps of treatment journey
    - Travel and cost must be considered
- Use of chemotherapy and associated side effects
  - Myeloablative conditioning utilized may cause reproductive harm
    - Reproductive health of patient must be discussed

Treatment Course Overview:

1- Determine if therapy is appropriate

- Weigh risks and benefits
- Discuss accessibility of treatment

2- Preparation for stem cell collection

- RBC transfusions
- Discontinue specific concomitant medications

3- Stem cell collection

- Mobilization: Medication given to help move blood stem cells from bone marrow into blood
- Apheresis: Separation and collection of stem cells from blood

4- Treatment production

- Stem cells edited accordingly
- Stem cells undergo testing

5- Conditioning and Infusion

- Chemotherapy followed by gene therapy

6- Follow up

- Short and long term monitoring

Casgevy Mechanism of Action

Gene editing

- Utilizes CRISPR/Cas9

Edits BCL11A gene

- Allows for higher production of fetal hemoglobin (HbF)
- Increases overall hemoglobin levels and decreases HbS concentration

Casgevy Safety Data

- Adverse reactions and incidence:
  - Febrile neutropenia= 48%
  - Mucositis= 86%
  - Decreased appetite= 41%
  - Musculoskeletal pain= 14%
  - Abdominal pain= 11%
  - Cholelithiasis= 11%
  - Pruritis= 11%
- Laboratory abnormalities and incidence:
  - Neutropenia= 100%
  - Thrombocytopenia= 100%
  - Leukopenia= 98%
  - Anemia= 84%
  - Lymphopenia= 50%
  - Hyperbilirubinemia= 14%

No reported case of GVHD, graft failure, or graft rejection

Casgevy Efficacy Data

Measured until at least 12 months after infusion

- Primary Endpoint:
  - Proportion of patients without severe VOC
    - 93.5% (n= 29/31)
- Secondary Endpoints:
  - Proportion of patients not hospitalized due to severe VOC
    - 100% (n= 30/30)
  - Median duration of severe VOC-free period
    - 22.2 months

Lyfgenia Mechanism of Action

Gene addition

- Modifies autologous CD34+ cells

Uses BB305 lentiviral vector to add βA-T87Q globin gene

- Now able to pair with α-globin to produce functional HbA
- Inhibits polymerization of HbS and reduces HbS levels

Lyfgenia Safety Data

- Adverse reactions and incidence:
  - Stomatitis= 71%
  - Febrile neutropenia= 44%
  - Decreased appetite= 11%
  - Pharyngeal inflammation= 11%
  - Nausea= 9%
  - Pyrexia= 7%
  - Bacteremia= 7%
- Laboratory abnormalities and incidence:
  - Thrombocytopenia= 69%
  - Neutropenia= 60%
  - Anemia= 33%
  - Leukopenia= 33%

Lyfgenia Safety Data

- Incidence of increased hepatic laboratory values:
  - Aspartate aminotransferase= 18%
  - Alanine aminotransferase= 13%
  - Gamma-glutamyl transferase= 13%
  - Blood bilirubin= 7%
- Black Box Warning: Hematologic malignancy
  - 1 patient developed acute myeloid leukemia and another developed myelodysplastic syndrome
    - Clinical trial resumed since both cases found to be unlikely related to vector

Lyfgenia Efficacy Data

Measured from 6 to 18 months post infusion

- Primary Endpoint:
  - VOE-CR (complete resolution of VOC)
    - 88% of patients (n= 28/32)
- Secondary Endpoint:
  - sVOE-CR (complete resolution of severe VOC)
    - 94% of patients (n= 30/32)

ICER Ratings

LYFGENIA	CASGEVY
B+: Incremental or Better	*C++: Comparable or Better*
Advantages:	**Advantages:**
• Improvement in severe SCD • Short-term improvements in clinical symptoms	• Similar benefits as Lyfgenia
Disadvantages:	**Disadvantages:**
• Uncertainties about duration of benefit • Potential harm from myeloablative conditioning and insertional oncogenesis	• Similar concerns to Lyfgenia about duration of benefit and harm • Uncertainty due to being first CRISPR therapy available • Uncertainty about generalizability of data due to small sample size

Clinical Pearls:

- Drugs to be discontinued:

Hydroxyurea	Disease-modifying agents	Iron chelators	Anti-retroviral
• 8 weeks prior to mobilization	• 8 weeks prior to mobilization	• 7 days prior to conditioning until 6 months post infusion	• 4 weeks prior to mobilization (for Lyfgenia specifically)

Clinical Pearls:

- Unspecified contraindications:
  - Lacking data for patients who have already undergone a hematopoietic cell transplant
- Monitoring Parameters:
  - Neutrophils, platelets, and CBC frequently until engraftment and recovery
  - Lyfgenia only: malignancy screening at least every 6 months post infusion

References:

Ataga KI, Kutlar A, Kanter J, et al. Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. N Engl J Med. 2017;376(5):429-439. doi:10.1056/NEJMoa1611770

Brandow AM, Liem RI. Advances in the diagnosis and treatment of sickle cell disease. *J Hematol Oncol*. 2022;15(1):20. Published 2022 Mar 3. doi:10.1186/s13045-022-01237-z

Brandow AM, Carroll CP, Creary S, et al. American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain. Blood Advances. 2020;4(12):2656-2701. doi:https://doi.org/10.1182/bloodadvances.2020001851

Centers for Disease Control and Prevention. (2024, May 15). Data and statistics on Sickle Cell Disease. Centers for Disease Control and Prevention. https://www.cdc.gov/sickle-cell/data/index.html

Exagamglogene Autotemcel [package insert]. Boston, MA: Vertex Pharmaceuticals; 2024

"FDA Approves First Gene Therapies to Treat Patients with Sickle Cell Disease." *U.S. Food and Drug Administration*, FDA, 8 Dec. 2023, www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapies-treat-patients-sickle-cell-disease.

Furstenau DK, Tisdale JF. Allogenic hematopoietic stem cell transplantation in sickle cell disease. Transfus Apher Sci. 2021 Feb;60(1):103057. doi: 10.1016/j.transci.2021.103057. Epub 2021 Jan 10. PMID: 33485798.

Lovotibeglogene Autotemcel [package insert]. Somerville, MA: Bluebird Bio Incorporated; 2023

Mangla, A. (2023, September 4). Sickle cell anemia. StatPearls NIH.

Mayo Foundation for Medical Education and Research. (2023, December 22). Sickle cell anemia. Mayo Clinic.

Niihara Y, Miller ST, Kanter J, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. N Engl J Med. 2018;379(3):226-235. doi:10.1056/NEJMoa1715971

"Sickle Cell Disease." ICER, 23 Jan. 2024, icer.org/assessment/sickle-cell-disease-2023/.

Wong TE, Brandow AM, Lim W, Lottenberg R. Update on the use of hydroxyurea therapy in sickle cell disease. Blood. 2014;124(26):3850-4004. doi:10.1182/blood-2014-08-435768

U.S. Department of Health and Human Services. (2024, August 28). What is sickle cell disease?. National Heart Lung and Blood Institute. https://www.nhlbi.nih.gov/health/sickle-cell-disease

CENTENE PHARMACY SERVICES

Questions?

CENTENE® Corporation