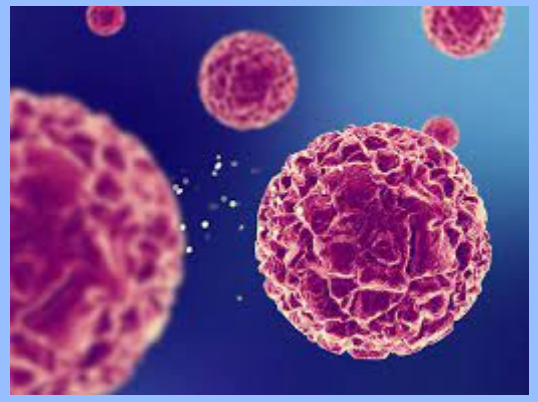
MSK Kids

Advances in gene therapy for the treatment of sickle cell disease

Joanne Torok-Castanza, RN, MSN, CPNP-PC, FNP, BMTCN

Date 12/09/22



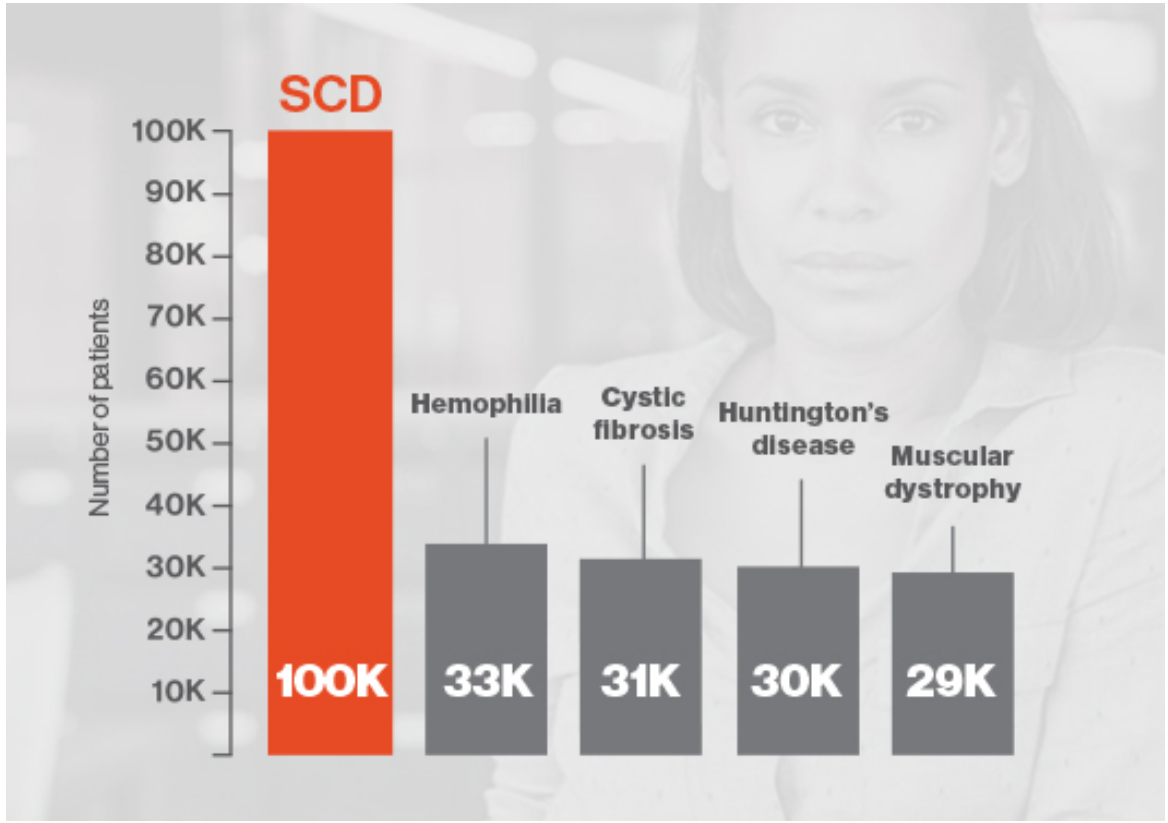
Memorial Sloan Kettering Cancer Center

Learning Objectives

- The learner will be able to describe the definition and pathophysiology of sickle cell disease
- The learner will be able to identify current supportive treatment of sickle cell disease.
- The learner will be able to understand and describe the mechanism of gene therapy for the treatment of sickle cell disease

Demographics and Scope of the Problem

- SCD is the most common genetic disorder globally
- 300000 infants are born annually with SCD
- 100000 Americans live with sickle cell disease. These numbers are projected to reach 400,000 by 2050.
- 1:365 Black Americans
- 1:16300 Hispanic Americans
- Most prevalent in Sub-Saharan Africa, South Asia, the Middle East, and the Mediterranean



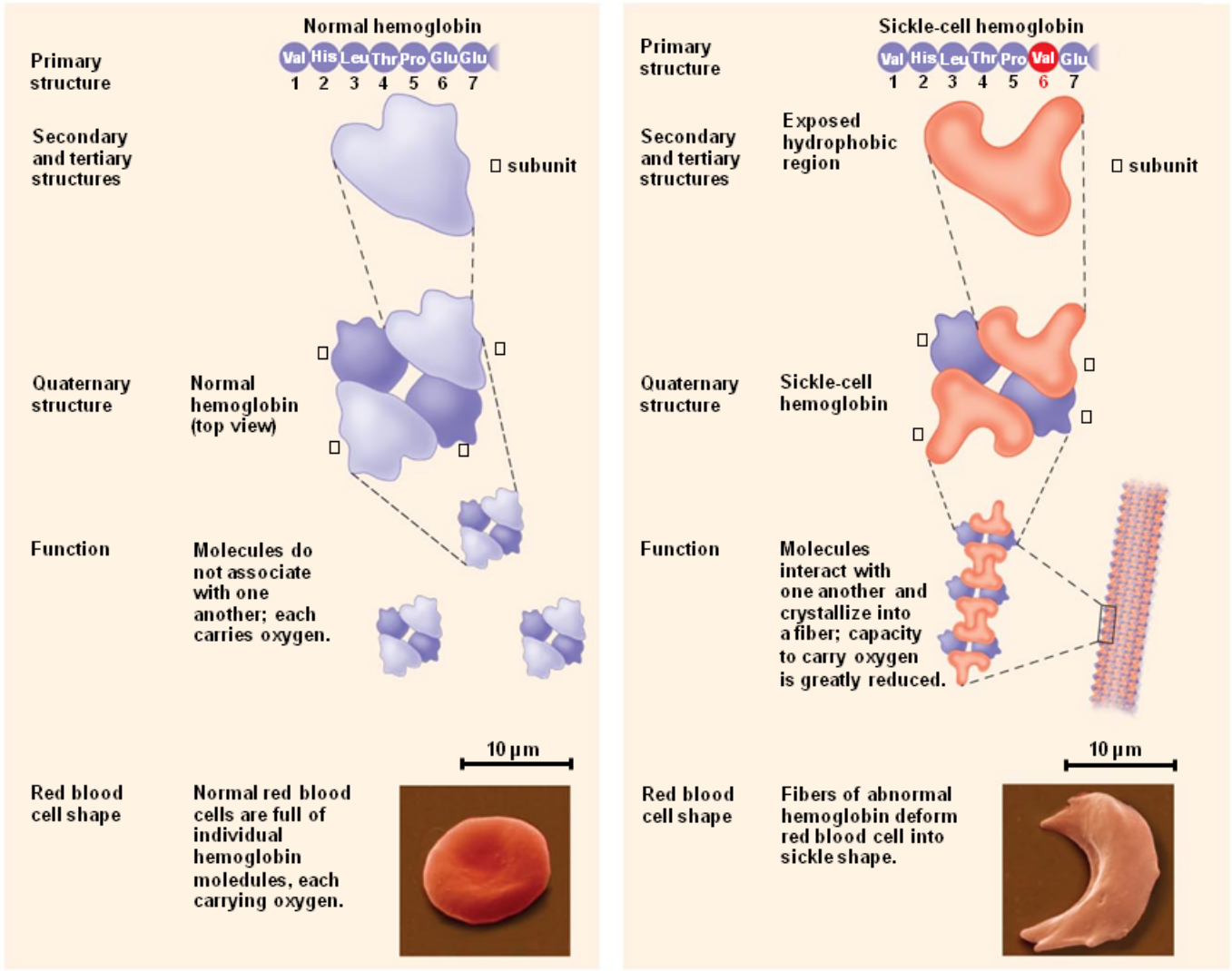
Data & Statistics on Sickle Cell Disease | CDC. (2022, May 2). Centers for Disease Control and Prevention.

What is Sickle Cell Disease?

- Sickle cell disease is a group of genetic disorders that can be progressively disabling and lead to chronic hemolytic anemia
- There is a single amino acid substitution at position 6 of Beta Globin chain of the hemoglobin molecule where valine is substituted for glutamic acid
- This single gene mutation results in changes in form and function of the hemoglobin molecule
- Sickled cells can lead to permanent damage of vessels, organs and bones
- Presence of fetal form of hemoglobin, HbF, persist for the first 6 months of life. Babies may not have clinic features of the disease until that time

Pathophysiology

Fig. 5-22



Sundd, P., Gladwin, M. T., & Novelli, E. M. (2019). Pathophysiology of Sickle Cell Disease. *Annual Review of Pathology: Mechanisms of Disease*, *14*(1), 263–292. https://doi.org/10.1146/annurev-pathmechdis-012418-012838

Hemoglobin S,C

Classification
Hgb S is the most prevalent form of SCD

- The inheritance of homozygous HbS is the most predominant form of SCD (referred to as HbSS)
- The next most common form of SCD is the co-inheritance of HbS and HbC—referred to as HbSC, this is most prevalent in Western Africa. The co-inheritance with β thalassaemia results in a sickle β thalassemia genotype (HbS/βo or HbS/β+), depending on the genetic lesion on the thalassemia component, the clinical presentation may be mild or equally as severe as homozygous SCD (HbSS)
- Those with HbS/βo-thalassaemia have a more severe course of disease similar to homozygous SS patients, while children with HbS/β+-thalassaemia depending on the β-globin mutation is associated with variable phenotype from mild to severe phenotypes SCD
- Hb S has a shorter lifespan 10-20 days vs 90=120 days for normal RBC

Triggers of SCD

Sudden change in temperature, particularly cold weather
Strenuous or excessive exercise
Dehydration
Infection
Emotional/Physical stress
High altitude
Alcohol
Smoking
Pregnancy
Uncontrolled Diabetes Mellitus

Treatment

- Though SCD was first discovered in the Western world in 1904 (had been recognized long before this in Africa), it was not until 1997 that the first drug (Hydroxyurea) was developed to treat the disease. It had been used as chemotherapy in the oncology setting for many years before that.

- Goals of treatment:
    - Management of VOC, chronic pain syndromes, chronic hemolytic anemia
    - Prevention and treatment of infections
    - Prevention of stroke
    - Management of the complications and various organ damage associated with SCD

Treatment/Medications

Hydroxyurea:

- First drug to be FDA approved for the treatment of SCD in 1997
- Mechanism:
  - Prevents the complications of SCD by increasing HbF and total hemoglobin concentrations. It decreases the adhesion of sickled cells to the endothelium
  - Large multicenter trial showed 44% reduction in VOC 2.5 years later
  - 9 year follow up to this study showed 40% reduction in SCD related mortality. It was found to be safe and efficacious in children

L-Glutamine:

- FDA approved in 2017 for the treatment of children over 5 with SCD
- The L-glutamine amino acid in Endari reduces oxidative stress and acute complications. It also participates in the formation of proteins, glutamate, amino sugars and nucleotides.

Treatment/Medications

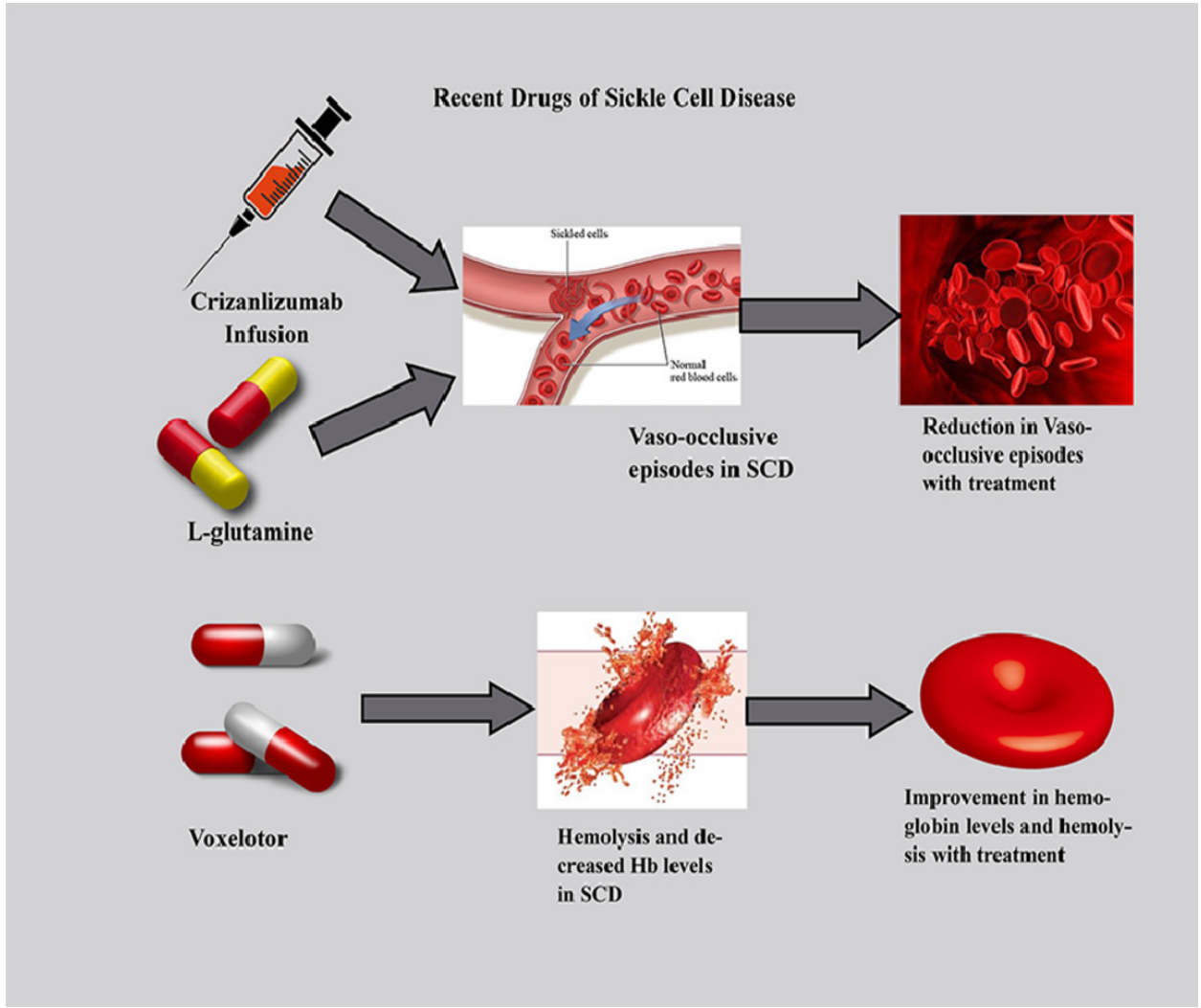
Voxelotor

- FDA approved in 2019 in patients over 12 years of age - First drug to target HgbS polymerization
- Binds reversibly to Hgb, stabilizing the oxygenated hemoglobin state and preventing HbS polymerization by increasing Hgb affinity for oxygen
- May inhibit sickling, reduce blood viscosity that contributes to anemia and hemolysis

Crizanlizumab

- FDA approved in 2019 for patients over 16 years of age
- Crizanlizumab is a humanized monoclonal antibody that binds to P-selectin and blocks its interaction with P-selectin glycoprotein ligand 1 (PSGL-1)
- P selectin contributes to adhesion of sickled red blood cells to blood vessels preventing flow through smaller vessels and leading to occlusive pain crises.

Comparison of Medication Treatment

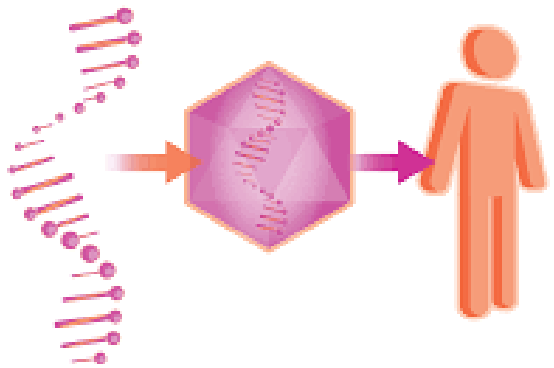


"Treatments, Therapies & Clinical Trials." *Sickle Cell Foundation of Minnesota*, https://www.sicklecellmn.org/scdtreatments.

Treatment/HSCT

- Only known cure for SCD
- 1986 and 2013: 1,000 patients received HLA-identical MSD HSCT
    - 93% overall survival
    - 16 years or older had worse overall survival (95% vs. 81% *p* = 0.001) and a higher probability of graft versus host disease
    - (GVHD)-free survival (77% >16y vs. 86% <16y)
- Who is eligible?
    - Patients with severe disease who have h/o:
        - stroke, acute chest syndrome, recurrent pain crisis, nephropathy, retinopathy, osteonecrosis of multiple joints and/or priapism
- Matched sibling transplants
    - Only 20% of patients with SCD will have a matched related and eligible donor.
    - Ethnic minorities are under represented in the BM registry making it difficult for patient with Hispanic, middle eastern and African ancestry to find unrelated donors.

How Gene Therapy Works



Peripheral Stem Cells Harvested from the patient by apheresis

Cells are genetically modified

Patient receives cytoreduction prior to re infusion

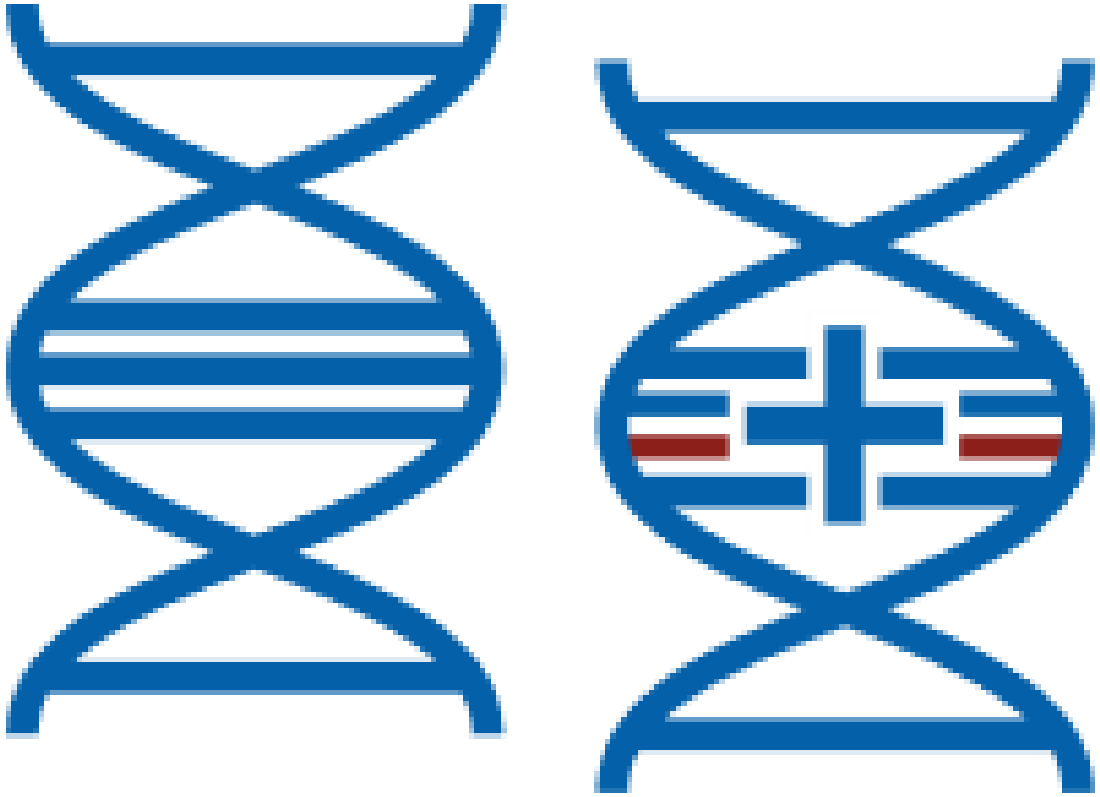
Autologous genetically modified stem cells are re infused into the patient

Why Gene Therapy for SCD?

- 70 years ago: SCD was at cutting edge of biomedical research as the first medical condition linked to a molecular cause – not until 1997 that Hydroxyurea was available to treat SCD
- Gene therapy is experimental at this point – Only HSCT is considered curative
- HSCT is known to be curative
    - Difficulty in finding well matched donors who are under-represented in African, Middle Eastern and South Asian groups (<20%)
    - Risk of graft failure and GVHD from allogeneic donors
    - Risk of fatal infection with compromised immune system
    - Gene therapy uses genetically modified autologous stem cells negating the risk of rejection and GVHD associated with HSCT
- Sickle cell disease presents a near ideal opportunity because the disorder arises from a mutation in a single nucleotide in one gene
- Targeted gene
    - Beta globin is the gene responsible for sickle cell
    - With gene editing, BCL11A can flip the switch and promote Hgb F production as used in gene editing

Types of Gene Therapy

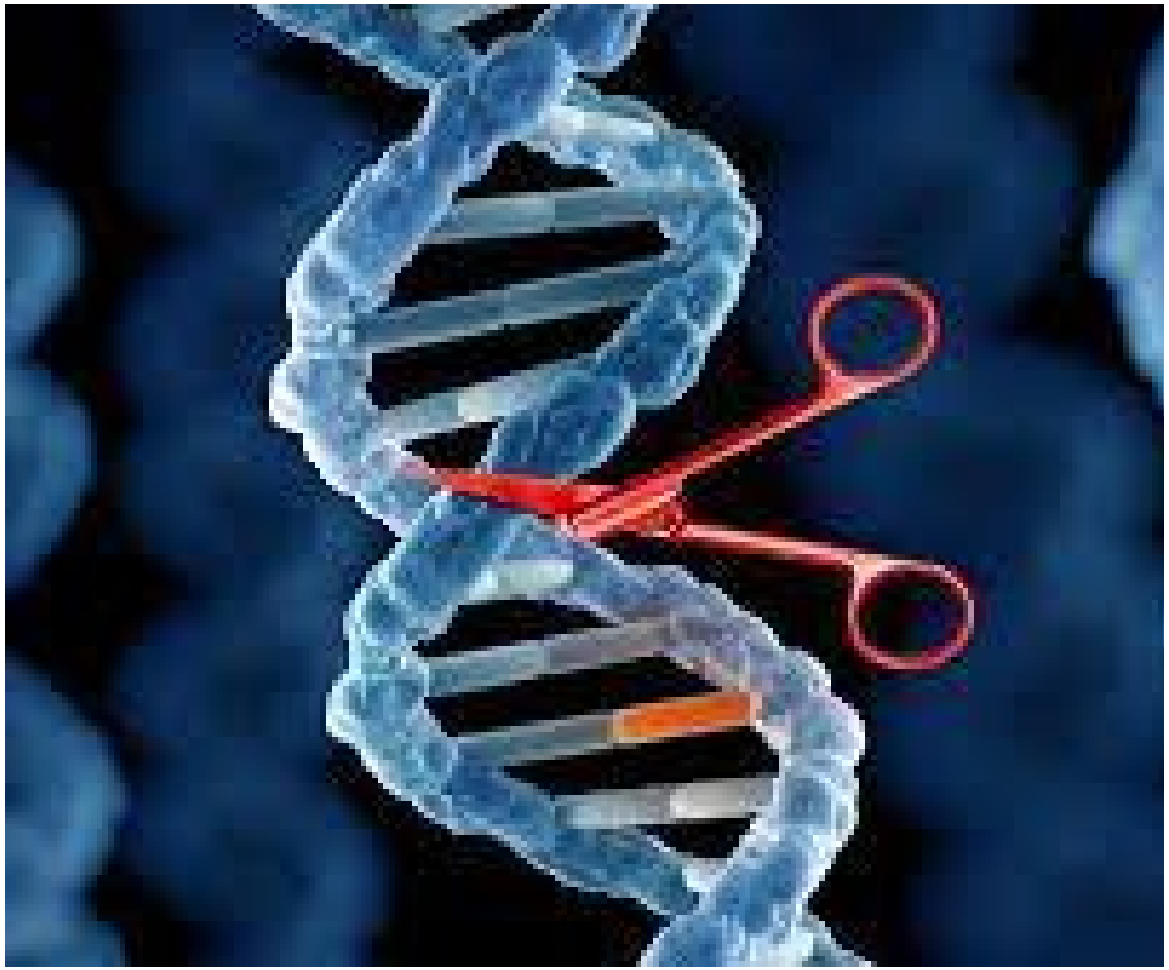
- Gene Addition:
    - Adds a working gene that instructs the body to produce a functioning form of hemoglobin that can compensate for sickle hemoglobin (HbS)
    - The native HbS gene is not altered
    - Results in production of both new hemoglobin and native HbS
    - Uses Lentiviral vectors to house and deliver a new gene



Types of Gene Therapy

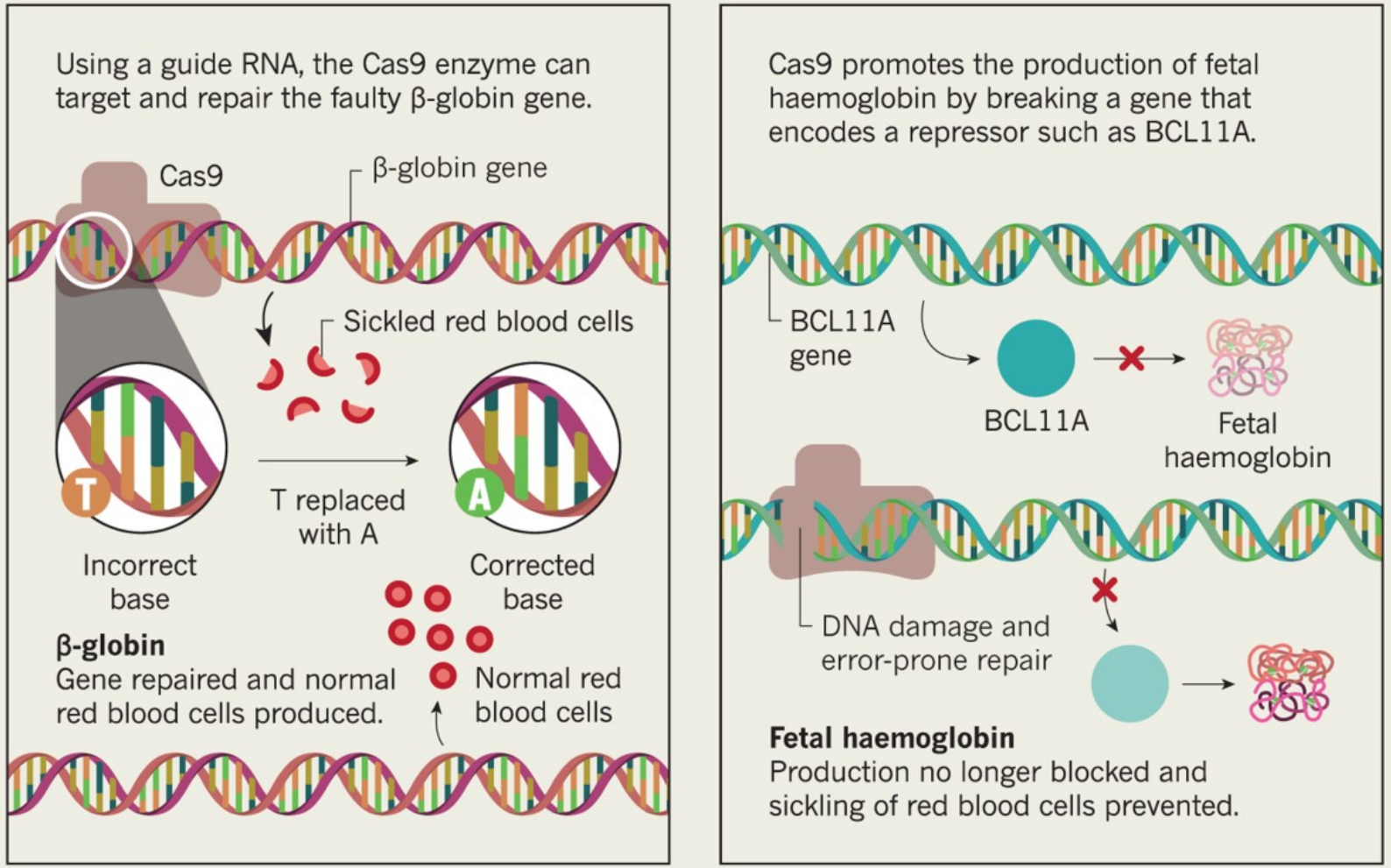
Gene Editing

- Most available method of gene therapy for SCD
- No viral vector
- Process of gene disruption that targets suppressors of HbF as a way to both increase HbF and decrease HbS
- Elements of DNA within a gene are targeted
    - Identifies and binds to the target with a highly specified enzyme to cut the DNA
    - Induces double stranded breaks.
    - This cut (electroporation) allows a change in the sequence with high precision resulting in an insertion or deletion
- Most current therapies using Gene Editing for SCD target BCL11A which is a negative regulator of HbF
    - Used to turn off the regulation of HbF in order to increase HbF production
    - CRISPR/Cas9 technology genome edited, expanded autologous stem cells



GENE EDITING WITH CRISPR

CRISPR–Cas9 gene editing is helping to tackle sickle-cell disease in two ways.



Bourzac, K. Gene therapy: Erasing sickle-cell disease. *Nature* **549**, S28–S30 (2017). https://doi.org/10.1038/549S28a

MSK Kids

Types of Gene Therapy

Gene Silencing

- Uses the regulation of gene expression in a cell to prevent the expression and resultant production of certain protein
- Similar to gene editing - this type of therapy is being used to suppress the *BCL11A* gene
- Results in an increase in HbF while reciprocally suppressing HbS production
- In contrast to gene editing, this type of gene therapy has relied on viral vector delivery (similar to gene addition) to deliver an antisense to messenger RNA to suppress the gene product instead of cutting the gene

Types of Gene Therapy

Gene Correction

- Can be performed in several different ways
- Includes a combination of gene editing and gene addition
- Most frequently - A guide RNA is used to identify the target mutation for cutting, and then editing occurs with the simultaneous delivery of template DNA of the correct sequence - inserted
- Currently the least efficient method
- Efforts are underway to improve gene correction
- Only type of gene therapy that aims to eliminate HbS production and introduce a non-sickling hemoglobin simultaneously

Initial Screening

- Initial screening occurs at least 18 months prior to infusion of genetically modified cells – Includes:
    - Comprehensive history and physical exam
    - Viral studies including Hep B, HIV, EBV, CMV, Parvovirus
    - Lab testing of HbF, ferritin, haptoglobin, general chemistries, pregnancy testing
    - EKG
    - PFT
    - Transcranial Doppler and Neurovascular MRI/MRA

Who is included?

Who is eligible?

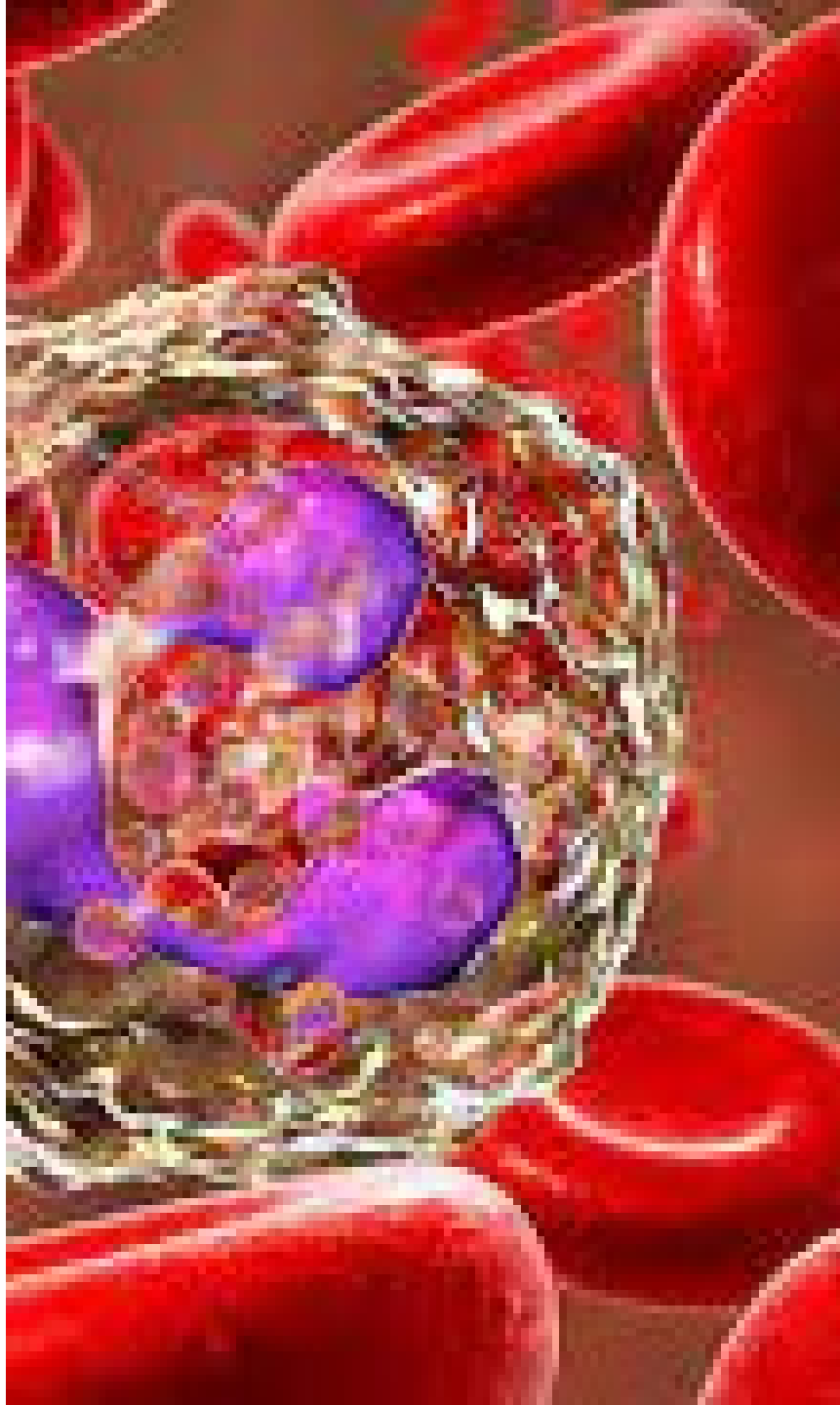
- Vaso occlusive pain crisis requiring analgesia - at least 3 episodes within 2 years
- Acute chest syndrome – at least 2 within 2 years
- Recurrent priapism – at least 2 within 2 years
- Patients receiving chronic transfusions to control complications of SCD
- Imaging evidence of prior CVA including both silent and overt stroke

Who is ineligible?

- Patients with a matched related donor
- Patients with a clinically significant active infection
- Patients who have had prior HSCT or gene therapy
- Patients with severe organ dysfunction
- Patients with contraindication to MRI

Process of gene therapy for SCD

- Preparation for apheresis
    - Once patients are eligible and have agreed to participate
    - Hydroxyurea is stopped for 2 months prior to apheresis
    - Patients receive weekly transfusion prior to apheresis for at least 2 months
    - Only patients on transfusion therapy >2 months can proceed to apheresis
- Apheresis
    - A large bore central line is inserted prior to apheresis
    - Plerixifor is used to mobilize stem cells
        - GCSF can induce a vaso occlusive crisis in patients with SCD
    - CD34+ stem cells are collected (15 x 10^6)
        - This includes enough cells to send to the manufacturing facility and a backup unit



Process of gene therapy for SCD

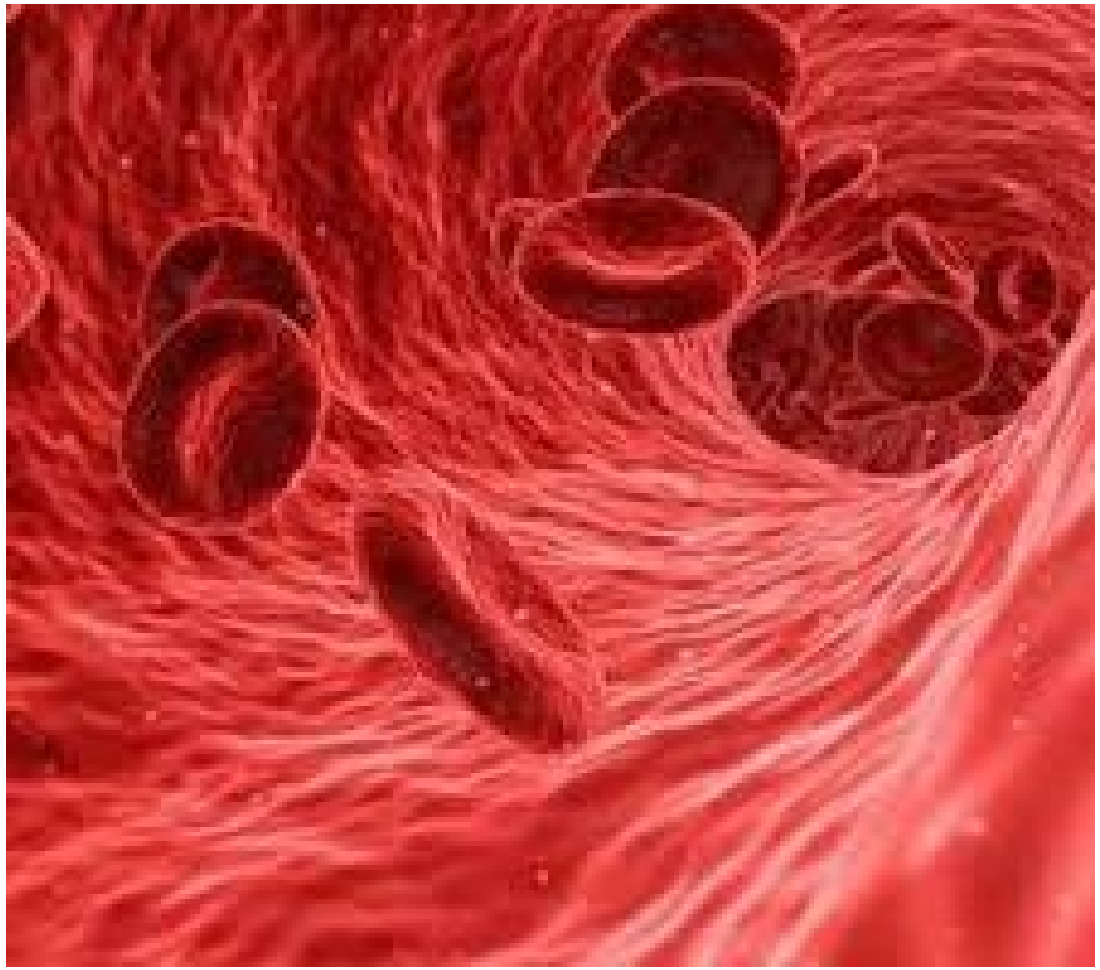
- Treatment following apheresis and prior to autologous stem cell infusion
    - Can resume hydroxyurea
    - Standard therapy and supportive care

- Once apheresis is completed and within 37 days from infusion pre treatment evaluation occurs
    - Dental and eye exams
    - CT Sinus, Spleen US, Transcranial doppler, Neurovascular MRI
    - EKG, Echocardiogram
    - PFTs
    - Age appropriate neurocognitive testing
    - Repeated viral serologies and chemistries

Cytoreduction and Infusion

- Cytoreduction:
  - Cytoreduction can start only if the stem cells are onsite
  - Myeloablative Conditioning
  - Busulfan or Treosulfan based regimens

- Infusion of cells:
  - At least one day of rest prior to infusion day (D 1)
  - Stem cells are either cryopreserved – thawed to room temperature prior to infusion or fresh depending on the company
  - 3.0-20.0 CD34+ cells/kg genetically altered autologous stem cells are infused

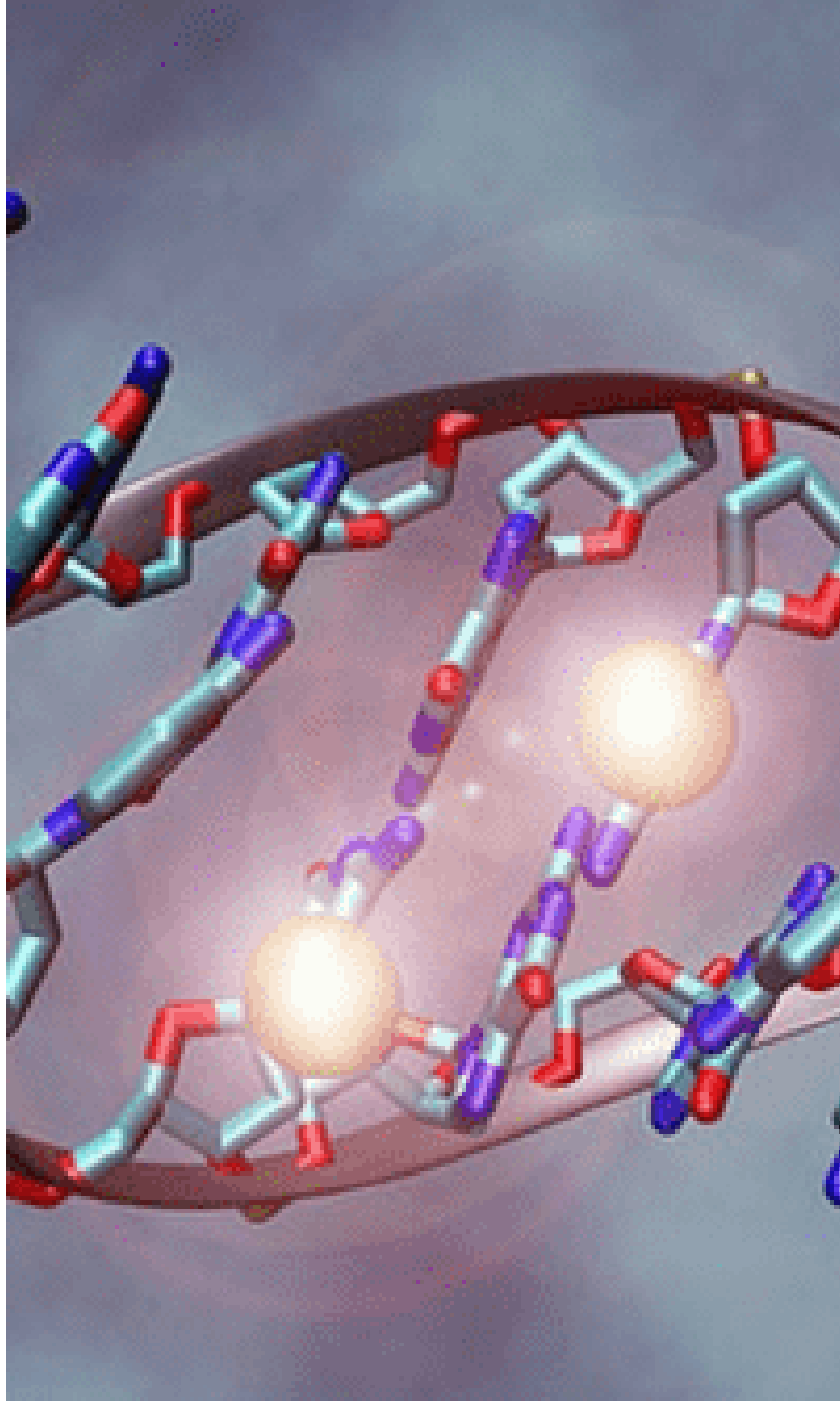


Early Clinical Study Results

- Most early clinical trials are based on data from viral vector based gene therapy
- Kanter et al (2022) NEJM : *Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease*
    - 43 patients were collected and 35 went on to receive a lentiglobin infusion with median follow up of 17.3 months
    - Engraftment occurred on all 35 patients
    - Median total Hb level increased from 8.5g/dL at baseline to 11g/dL – 6 to 36 months following infusion
    - Hemolysis markers were reduced
    - Among the 25 patients who could be evaluated, all had resolution of severe VOC events as compared to median of 3.5 events per year (range of 2-13) in the past 24 months prior to enrollment
    - 3 patients had nonserious adverse events related or possibly related to LentiGlobin that resolved within one week of onset
    - No cases of hematologic cancer were observed during the 37.6 months of follow up

Treatment related risks

- Off target gene editing
    - Creation of a genetic change that leads to malignant transformation to leukemia/lymphoma
    - None have been detected with use of CRISPR/electroporation
    - Bluebird Bio paused phase I/II Studies in Europe after one patient developed AML and one MDS after receiving their product that utilized a deactivated viral vector – was later proven to be unrelated to the viral vector
        - These patients are being closely followed
        - Patients with sickle cell disease have a 72% increased risk of developing leukemia over the general population
        - Patients received alkylating agents prior to transplant in the setting of chronic lifelong inflammation, stem cells are in a weakened state increasing the potential for malignant disease



Treatment Related Risks

- Graft failure
    - Failure to reach an ANC of 500 consistently for 3 days by day 45
    - Occurs in <1% of patients
- Impaired fertility
    - Use of alkylating agents in conditioning regimen impairs fertility in both men and women
    - Males can choose to cryopreserve sperm or testicular tissue
    - Females can choose to cryopreserve oocytes released after hormonal stimulation or ovarian tissue obtained by surgical biopsy
    - Patients of child bearing age must use contraception until 6 months after infusion for females and 3 months for males due to unknown fetal effects of therapy
- Secondary Malignancy due to conditioning regimens

Final Take Home

- Gene therapy for sickle cell disease is promising
- It is still considered experimental and not yet FDA approved, but will hopefully be FDA approved soon
- Gene Therapy has been FDA approved for the treatment of Thalassemia
- Only known curative option currently is HSCT with gene therapy yet to be determined

Hertz Nazaire: Sickle cell warrior who raised sickle cell awareness through art

Thank you!!

Questions?

References

Bourzac, K. (2017). Gene therapy: Erasing sickle-cell disease. *Nature* **549**, S28–S30 (2017). https://doi.org/10.1038/549S28a

Data & Statistics on Sickle Cell Disease | CDC. (2022, May 2). Centers for Disease Control and Prevention. https://www.cdc.gov/ncbddd/sicklecell/data.html#:%7E:text=SCD%20affects%20approximately%20100%2C000%20Americans,sickle%20cell%20trait%20(SCT).

Kanter, J., & Falcon, C. (2021). Gene therapy for sickle cell disease: where we are now? *Hematology*, *2021*(1), 174–180. https://doi.org/10.1182/hematology.2021000250

Kanter, J., Walters, M. C., Krishnamurti, L., Mapara, M. Y., Kwiatkowski, J. L., Rifkin-Zenenberg, S., Aygun, B., Kasow, K. A., Pierciey, F. J., Bonner, M., Miller, A., Zhang, X., Lynch, J., Kim, D., Ribeil, J. A., Asmal, M., Goyal, S., Thompson, A. A., & Tisdale, J. F. (2022). Biologic and Clinical Efficacy of LentiGlobin for Sickle Cell Disease. *New England Journal of Medicine*, *386*(7), 617–628. https://doi.org/10.1056/nejmoa2117175

Jain, S., Bakshi, N., & Krishnamurti, L. (2017). Acute Chest Syndrome in Children with Sickle Cell Disease. *Pediatric Allergy, Immunology, and Pulmonology*, *30*(4), 191–201. https://doi.org/10.1089/ped.2017.0814

References:

Sundd, P., Gladwin, M. T., & Novelli, E. M. (2019). Pathophysiology of Sickle Cell Disease. *Annual Review of Pathology: Mechanisms of Disease*, *14*(1), 263–292. https://doi.org/10.1146/annurev-pathmechdis-012418-012838

Novelli, E. M., & Gladwin, M. T. (2016). Crises in Sickle Cell Disease. *Chest*, *149*(4), 1082–1093. https://doi.org/10.1016/j.chest.2015.12.016

Hsieh, M. M., Bonner, M., Pierciey, F. J., Uchida, N., Rottman, J., Demopoulos, L., Schmidt, M., Kanter, J., Walters, M. C., Thompson, A. A., Asmal, M., & Tisdale, J. F. (2020). Myelodysplastic syndrome unrelated to lentiviral vector in a patient treated with gene therapy for sickle cell disease. *Blood Advances*, *4*(9), 2058–2063. https://doi.org/10.1182/bloodadvances.2019001330

Eisenstein, M. (2021). Gene therapies close in on a cure for sickle-cell disease. *Nature*, *596*(7873), S2–S4. https://doi.org/10.1038/d41586-021-02138-w