DECISIONS, DECISIONS, DECISIONS: WHICH TREATMENT IS RIGHT FOR ME OR MY CHILD?

SCDAA'S 48TH ANNUAL NATIONAL CONVENTION 2020

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Research Funding and Consultancy

Global Blood Therapeutics

Novartis Pharmaceuticals

Bluebird Bio

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Overview of Presentation

- Background: Timeline of Therapies in SCD
- Background: Complications in Sickle Cell Disease
- Review of current disease modifying therapies and clinical trials
- Review of new mechanisms of action for new disease modifying therapies
- Considerations and Clinical Scenarios for therapies in SCD
- Review current FDA approved treatments and Curative therapies

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Future for new therapies are Bright for SCD!

- There are over 20 new therapeutic products under investigation for SCD

- These include Bone Marrow Transplant and Gene Therapies

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Time of therapies in SCD

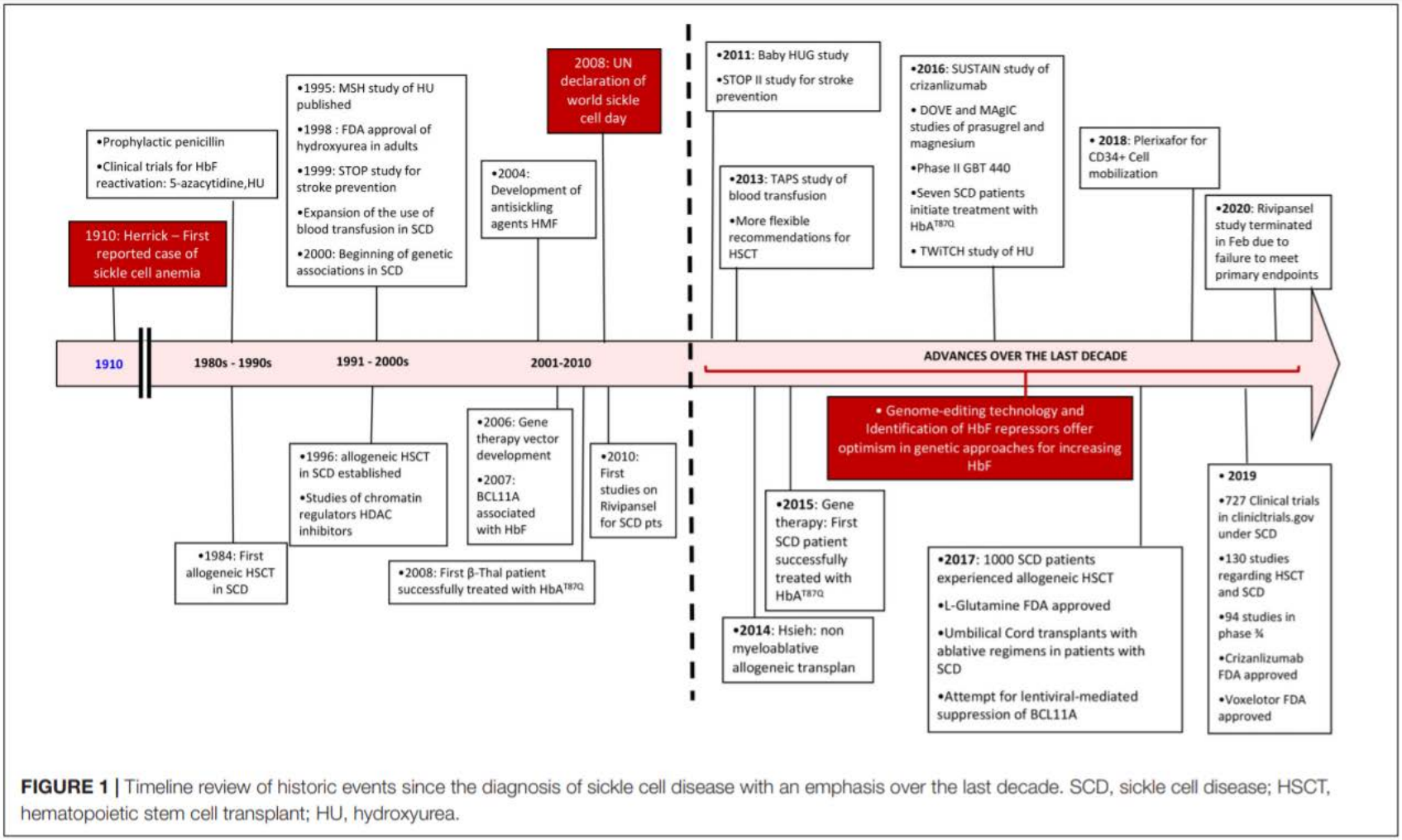

FIGURE 1 | Timeline review of historic events since the diagnosis of sickle cell disease with an emphasis over the last decade. SCD, sickle cell disease; HSCT, hematopoietic stem cell transplant; HU, hydroxyurea.

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Background: Novel Therapeutics for SCD

- New Approaches to SCD Therapies have shifted in many ways in the past 5-10 years.

- ***1) Renewed Focus on what's Outside the RBC***

- ***2) What's really happening inside the Sickle Red Blood Cell? Other mechanisms that trigger sickling.***

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CASE

16 y/o male with Hgb SS Sickle cell disease who is maintained on hydroxyurea @ 25mg/kg/day with Hgb 8.5 and fetal hemoglobin(Hgb F) of 25% (MCV 100) and has had an increase in pain in his lower legs x 6 mos. What should we do to optimize his sickle cell care?

What are his treatment options??

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Considerations: What's happening in the sickle cell patient? What complications exist now or happen recurrently ?

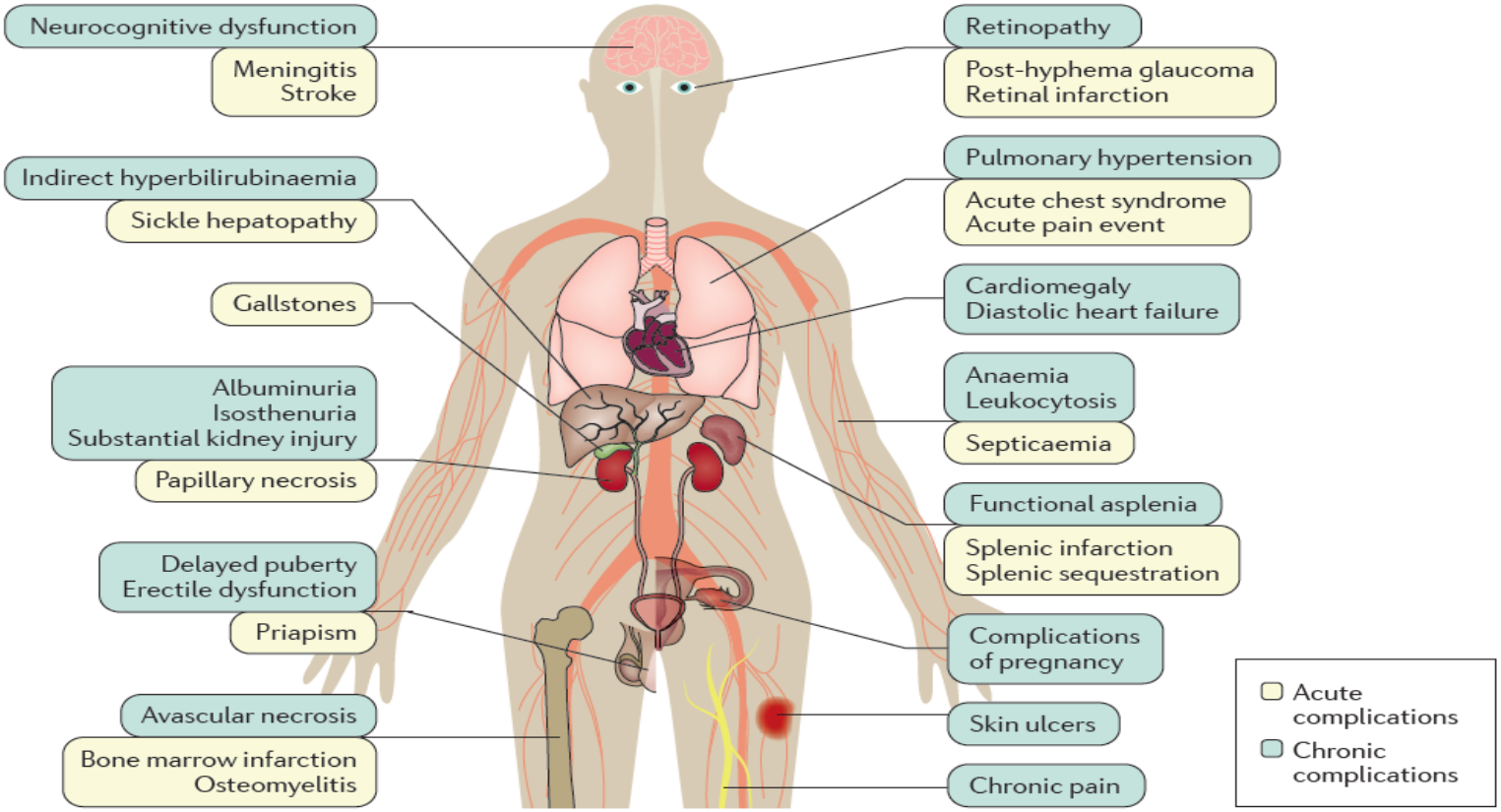

Figure 5 | **Sickle cell disease clinical complications.** Acute complications bring the individual with sickle cell disease (SCD) to immediate medical attention; pain is the most common acute complication. As individuals with SCD age, chronic complications produce organ dysfunction that can contribute to earlier death. Complications of pregnancy include pre-eclampsia, intrauterine growth restriction, preterm delivery and perinatal mortality.

Overall Complications in an aging SCD patient

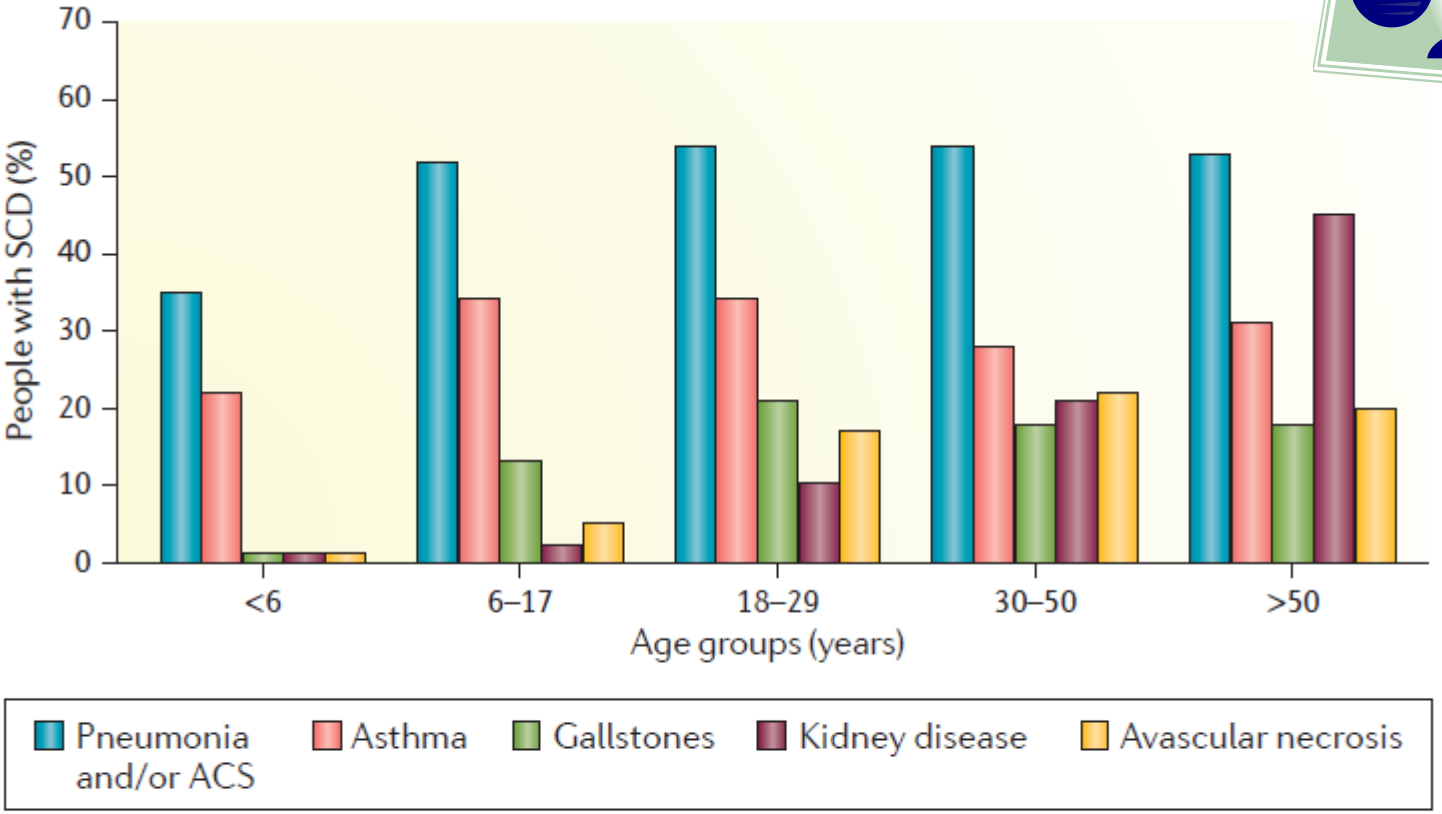

Figure 6 | **Age distribution of chronic sickle cell disease complications.** Development of clinical complications in 5,100 individuals with sickle cell disease (SCD) identified in the California Hemoglobinopathy Surveillance Program[271]. ACS, acute chest syndrome.

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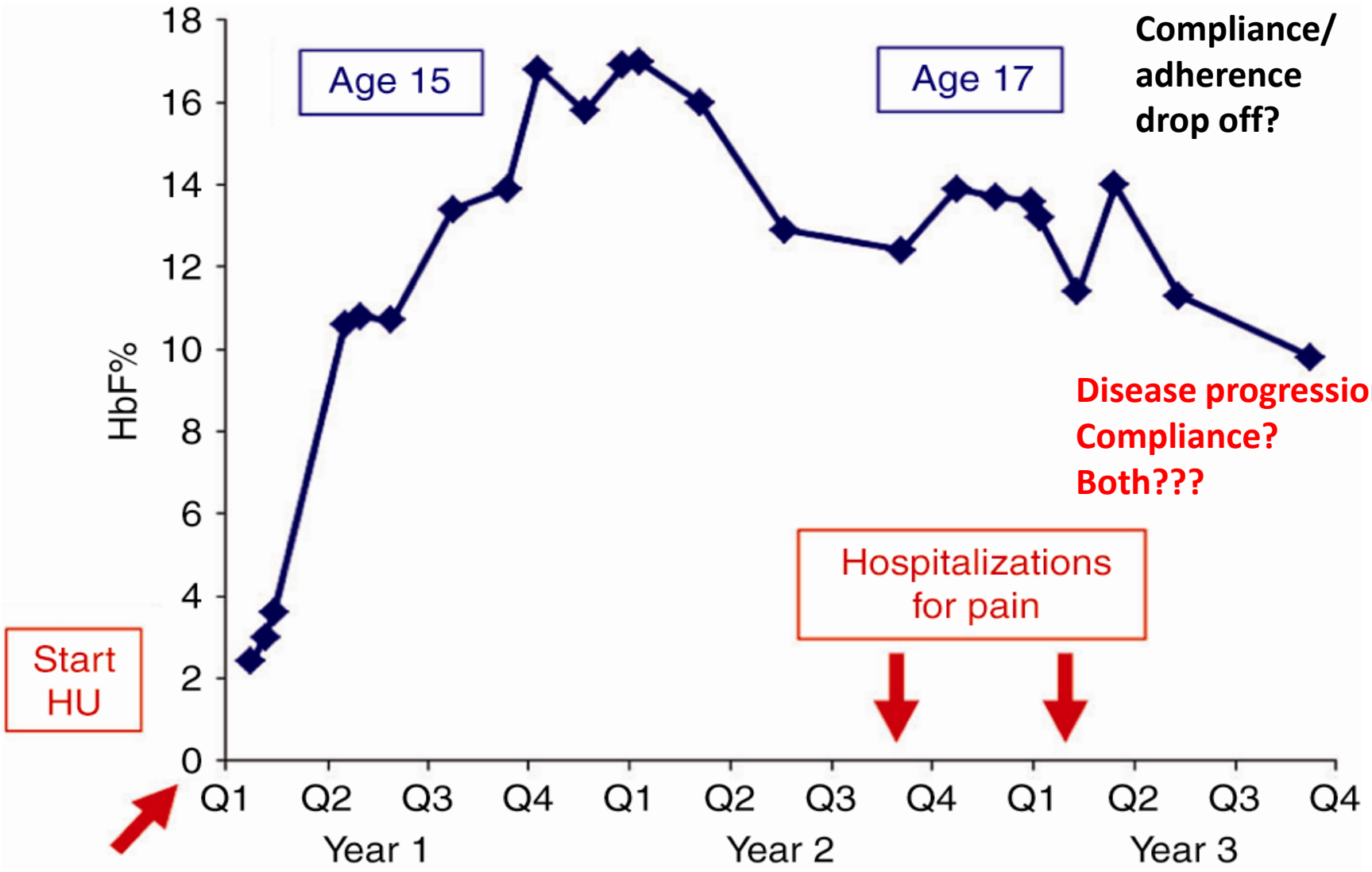
Considerations for the type of treatment: Age, How is it given, side effects, indications

- **Considerations**
  - Age eligibility(2 y/o, 5 y/o, 12 y/o, 16, y/o, 18 y/o)
  - Route of delivery(oral vs IV); tablet vs solution
  - Side Effect Profile
- **Indications**
  - Prevention of ongoing end organ damage
  - Decrease the frequency of symptoms/complications
    - Pain episodes
    - Acute chest syndrome
    - Priapism
    - Lack of energy

Compliance/Adherence



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AYA Transition Considerations and Compliance→ where will you go?

- Adults who had died, the average time between transfer of care and death was 1.8 years (Quinn et al, 2010).
- 2-3 Fold increase Mortality of SCD patients >18 years vs their younger pediatrics
- Unfortunately, this period of transition is often defined by patients “lost to follow up” due to
    - Poor acceptance of new adult healthcare providers
    - non-adherence to disease-modifying treatments such as hydroxyurea
    - sharp increases in rates of hospitalization and readmission
    - Lack of Adult Hospitals caring for SCD patients
    - Lack of Geographic Regional Clinics and Hospitals

SICKLE CELL DISEASE- Types of Therapies

- **Categories**
  - **Disease Modifying**
    - Change the course of the disease without cure
      - Hydroxyurea
      - Oxbryta
      - Adakveo
      - Endari-L Glutamine
  - **Curative therapies**
    - **Bone Marrrow(Stem Cell) Transplantation**
      - Sibling match
      - Haplo(Half match, i.e. parent) identical match
      - Match Unrelated Donor
  - **Gene Therapy**

SICKLE CELL DISEASE- Types of Therapies

- Quality of Life
  - Effective in improving or maintaining a acceptable quality of life

Risks and Benefits

- Side effects→ acceptable??
- Short term risks→ GI,strokes
- Long term risks-->
- Development of another chronic disease(i.e GVHD) or worsening the health of another organ (i.e. kidney)
- Mortality(chance of dying from this therapy)

- Reproductive health
  - Spermatogenesis/ sperm count
  - Oocyte(eggs) damage
  - Sperm collection pre BMT
  - Oocyte(eggs) preservation pre BMT/?

SICKLE CELL DISEASE- Clinical Scenarios

- **Clinical Scenarios**
  - **Low Hemoglobin(.i.e Hgb <9.0) on Maximum Tolerated Dose on hydroxyurea**
    - **Oxbryta**
  - **Persistent Pain on hydroxyurea on Maximum Tolerated Dose on hydroxyurea**
    - **Adakveo**
    - **L-Glutamine**
  - **Development of severe red blood cell antibodies or history of Hyperhemolysis**
    - **Erythropoietin +/- hydroxyurea**
    - **Volexotor**

Summary of Recommended Treatment Approaches for Sickle Cell Disease before 2019

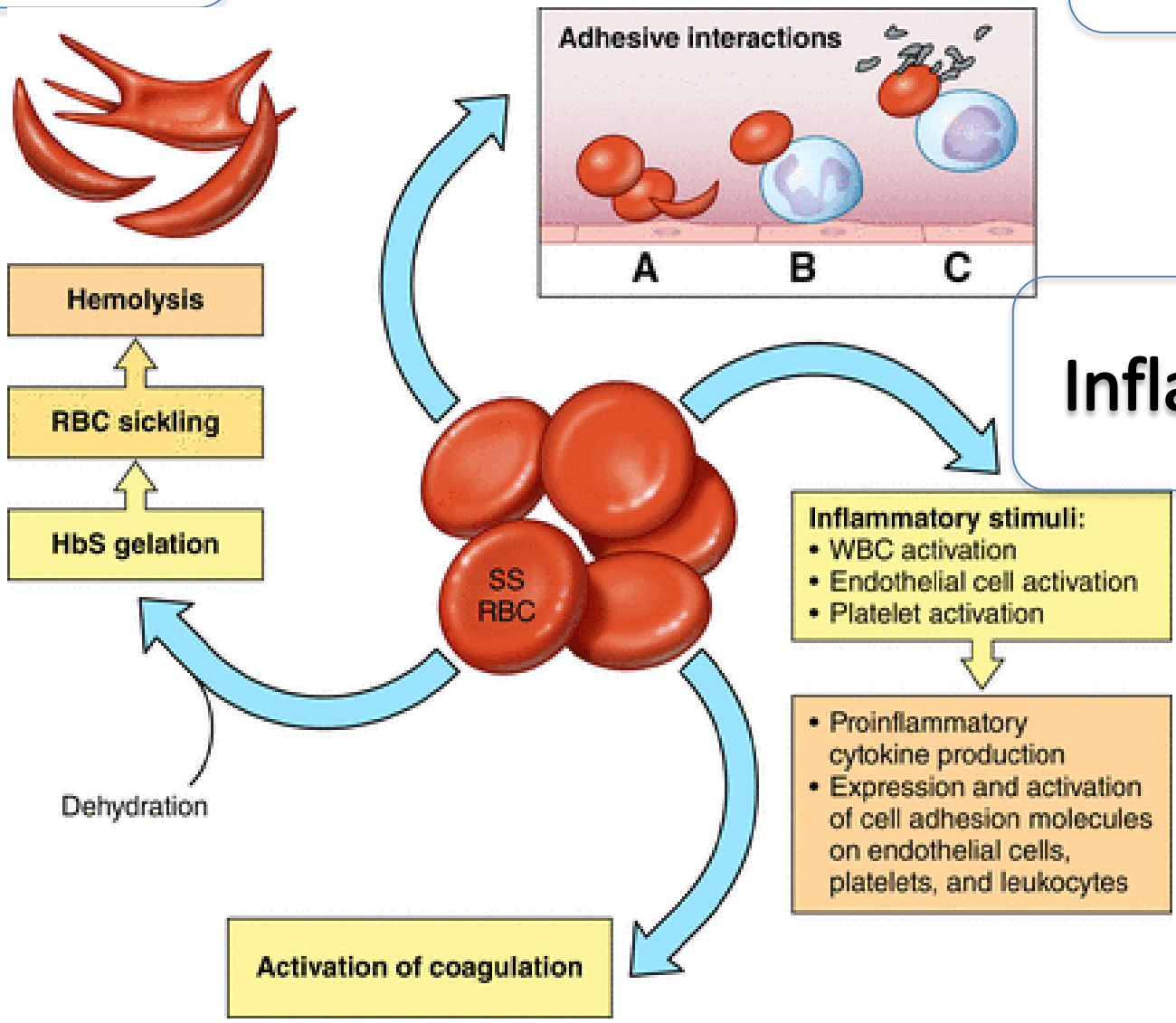
Table 1. Summary of Recommended Treatment Approaches for Sickle Cell Disease.*

Treatment Approach	Dose and Frequency	Duration	Recommendation	Evidence Quality	Availability in Low-Resource Areas
Prevention of infection					
Penicillin V	62.5–250 mg, twice daily	At least until 5 yr of age	Strong	Moderate	Available
Pneumococcal vaccines	Every 5 yr, starting at 2 yr of age	Lifelong	Strong	Moderate	Limited availability
Malarial prophylaxis when appropriate	Daily (e.g., proguanil), weekly (e.g., pyrimethamine), or intermittent (e.g., mefloquine–artesunate or sulfadoxine–pyrimethamine plus amodiaquine)	Lifelong (in malarious area)	Strong	Low	Available
Blood transfusion					
Acute care					
Treatment of anemia	Simple transfusion; target hemoglobin level, 10 g/dl	Limited	Strong	Low	Limited availability
Preoperative transfusion (if hemoglobin <8.5 g/dl)	Simple transfusion, performed once; target hemoglobin level, 10 g/dl		Strong	Moderate	Limited availability
Ongoing care					
Primary stroke prevention	Target HbS, <30%; transfusions every 3–6 wk	Indefinite	Strong	High	Very limited availability
Secondary stroke prevention	Target HbS, <30% or <50%; transfusions every 3–6 wk	Indefinite	Moderate	Low	Very limited availability
Prevention of additional silent cerebral infarctions	Target HbS, <30%; transfusions every 3–6 wk	Indefinite	Moderate	Moderate	Very limited availability
Hydroxyurea					
Universal use	20–35 mg/kg/day	Indefinite	Moderate	Moderate	Limited availability
Prevention of acute complications	15–35 mg/kg/day	Indefinite	Strong	High	Limited availability
Primary stroke prevention	15–35 mg/kg/day	Indefinite	Strong	Moderate	Limited availability

* Data on recommended treatments, the strength of the recommendation, and the quality of the evidence are from DeBaun et al.,[10] Ware et al.,[11] and Yawn et al.[12] Data on availability in low-resource areas are from Bello-Manga et al.[13] HbS denotes sickle hemoglobin.

Hemolysis

Adhesion



Inflammation

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Complexity of our new understanding of Sickle Cell Disease Pathophysiology:So many factors!!

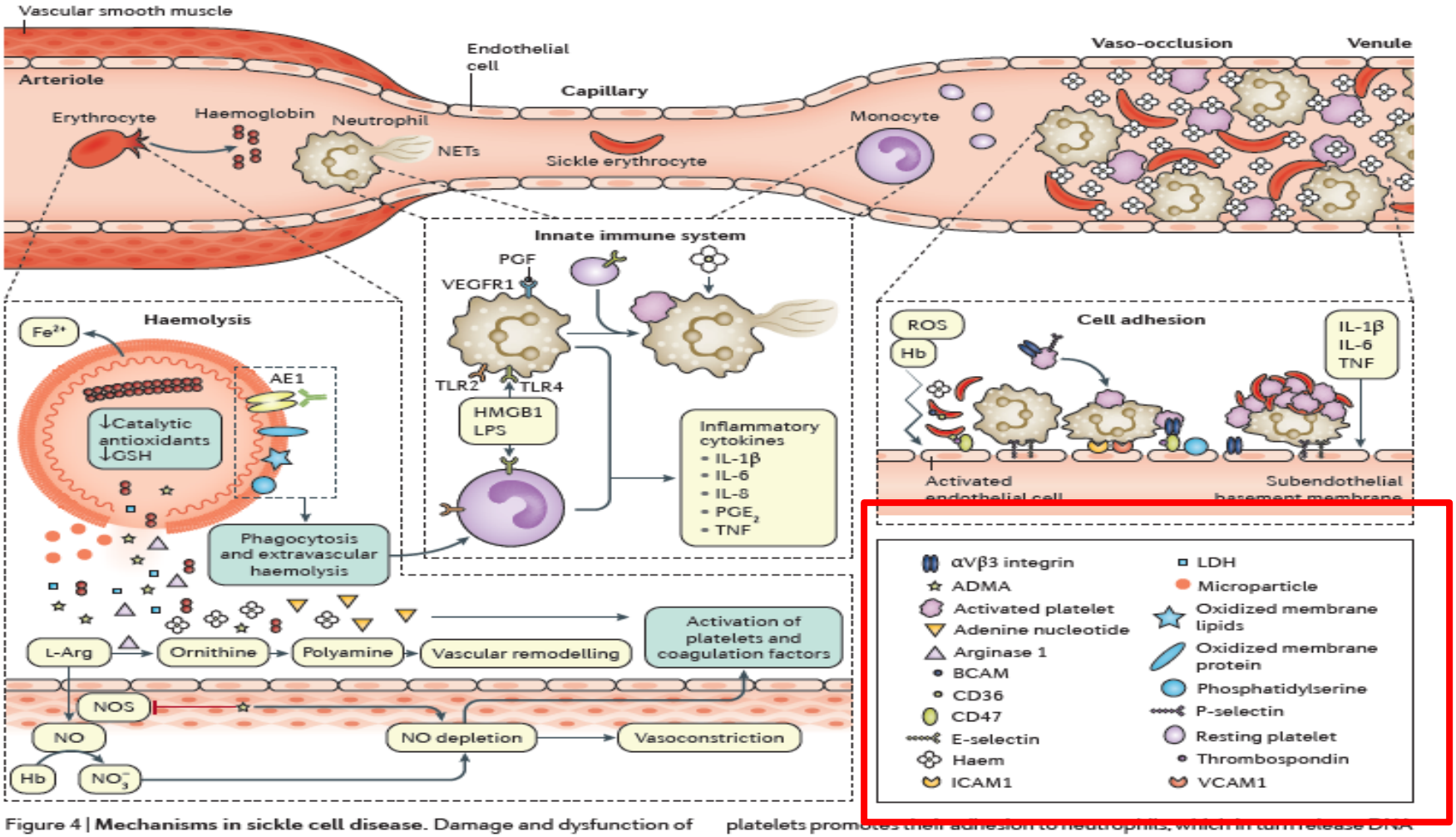

Figure 4 | **Mechanisms in sickle cell disease.** Damage and dysfunction of the erythrocyte membrane caused by sickle haemoglobin (HbS) platelets promotes their adhesion to neutrophils, which in turn release DNA to form neutrophil extracellular traps (NETs). Circulating blood cells adhere

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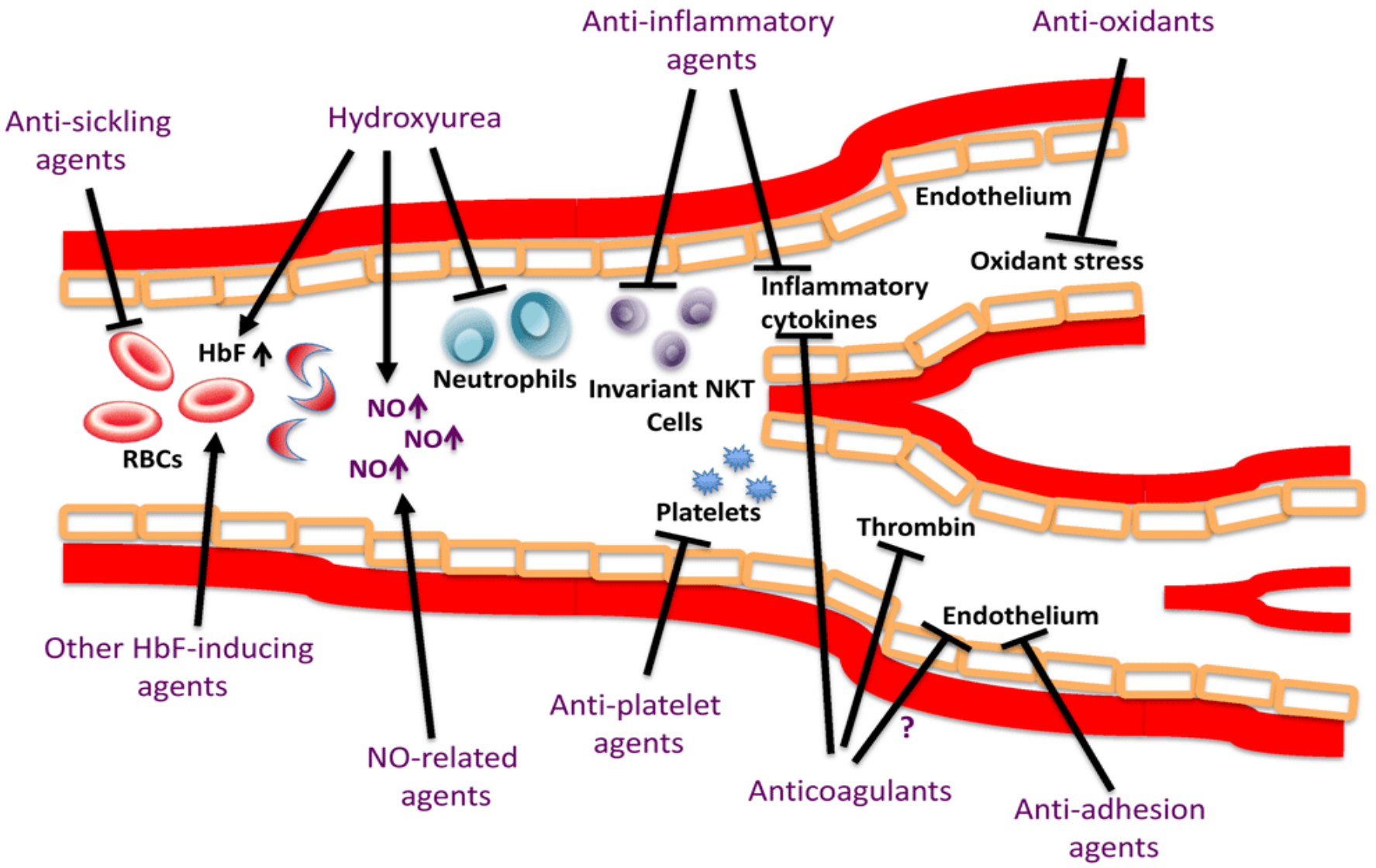
How do new sickle cell treatments work in SCD?



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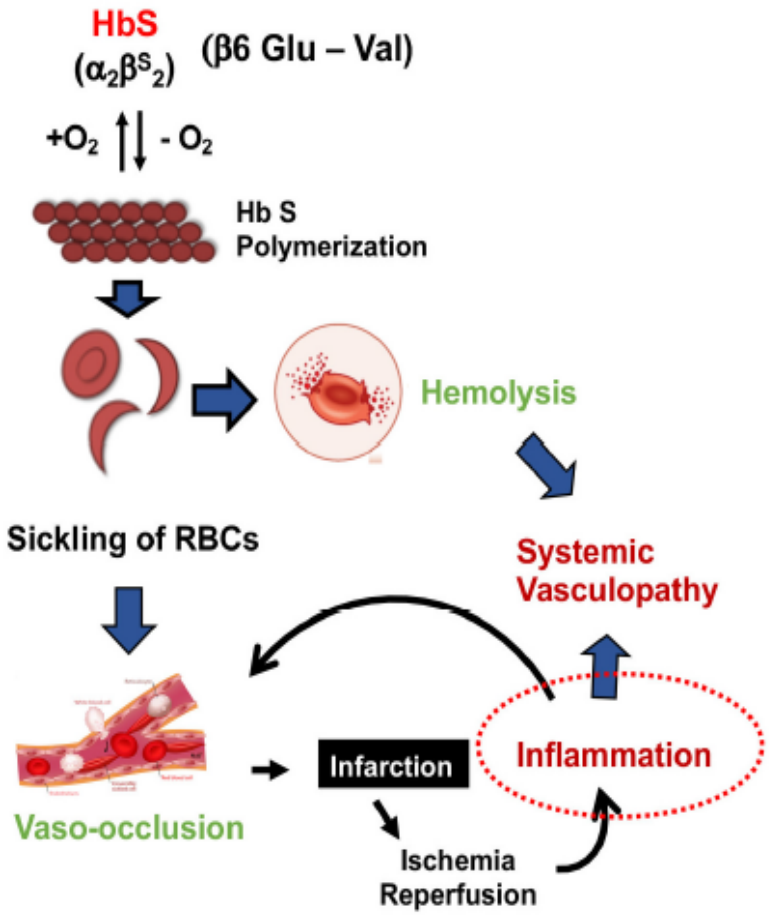
Targets of Treatments for SCD

Targeting Pathobiology of Sickle Cell Disease



Change the genotype

- Allogeneic BMT –
- Autologous HSCT modification

Target HbS polymerization

- Increase Fetal hemoglobin
  - ❖ Genetic and genomic approaches
    - Suppressing BCL11A
    - Simulate HPFH variants
  - ❖ Pharmacologically– eg. hydroxyurea
- Hb O2 affinity

Targeting Vaso-occlusion

- Inhibiting adhesive interactions between cells and endothelium

Targeting Inflammation

- Feedback loop of sterile inflammation that promotes further vaso-occlusion
- L-glutamine
- Inflammasome inhibition

FIGURE 2 | Schematic pathophysiology review of sickle cell disease and its main different targets for intervention. Hb S, hemoglobin S.

Sickle Cell FDA Approved Drugs (4)

		FDA Approved	Age
Endari(L-Glutamine)	Anti-Oxidant	2017	5 years and older
Hydroxyurea	Increases Fetal Hemoglobin Anti-Inflammatory Anti-Adhesion	Adults 1998 Children 12/2017	18 y/o and older 2 years and older
Oxbryta(Voxelotor)	Increases Hemoglobin Red Blood Cell Allosteric Modifier (increases O2 to Sickle Cells	Children and Adults 11/2019	12 years and older
Adakveo(Crizanlizumab)	Anti-Adhesion	Children and Adults 11/2019	16 years and older

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Stages of Different Treatments Options from Clinical Trials→ Standard of care/FDA

Medication	Mechanism of Action	Early Stages	Phase 2	Phase 3	Standard of care
Hydroxyurea	Targeting Hb S polymerization: increasing Hb F	→	→	→	→
*L-Glutamine (Endari) – FDA approved July 2017	Targeting vasoocclusion: Increase NAD and NADH and decrease adhesion	→	→	→	→
**Crizanlizumab (Adakveo) – FDA approved November 2019	Targeting vasoocclusion: P-selectin inhibition	→	→	→	→
**Voxelotor/ GBT440 (Oxbryta) – FDA approved November 2019	Targeting Hb S polymerization: increasing oxygen affinity	→	→	→	→
HLA-matched transplant	Modify the genotype	→	→	→	→
Haploidentical transplant	Modify the genotype	→	→	→	
***Rivipansel	Targeting vasoocclusion: Pan-selectin inhibition	→	→	→	

Medication	Mechanism of Action	Early Stages	Phase 2	Phase 3	Standard of care
Sevuparin	Targeting vasoocclusion: Pan-selectin inhibition	→	→		
N-Acetylcisteine	Targeting inflammation: Antioxidant effect	→	→		
IMR-687	Targeting Hb S polymerization: inhibiting PDE9	→	→		
Sanguinate	Targeting Hb S polymerization: carbon monoxide delivery	→	→		
CRISPR-Cas9 modified CD34+	Modify the genotype	→			
Gamma-globin gene transfer	Modify the genotype	→			
Lentiglobin bb305	Modify the genotype	→			
Lentivirus shRNA targeting BCL11a	Modify the genotype	→			

Blood Transfusion

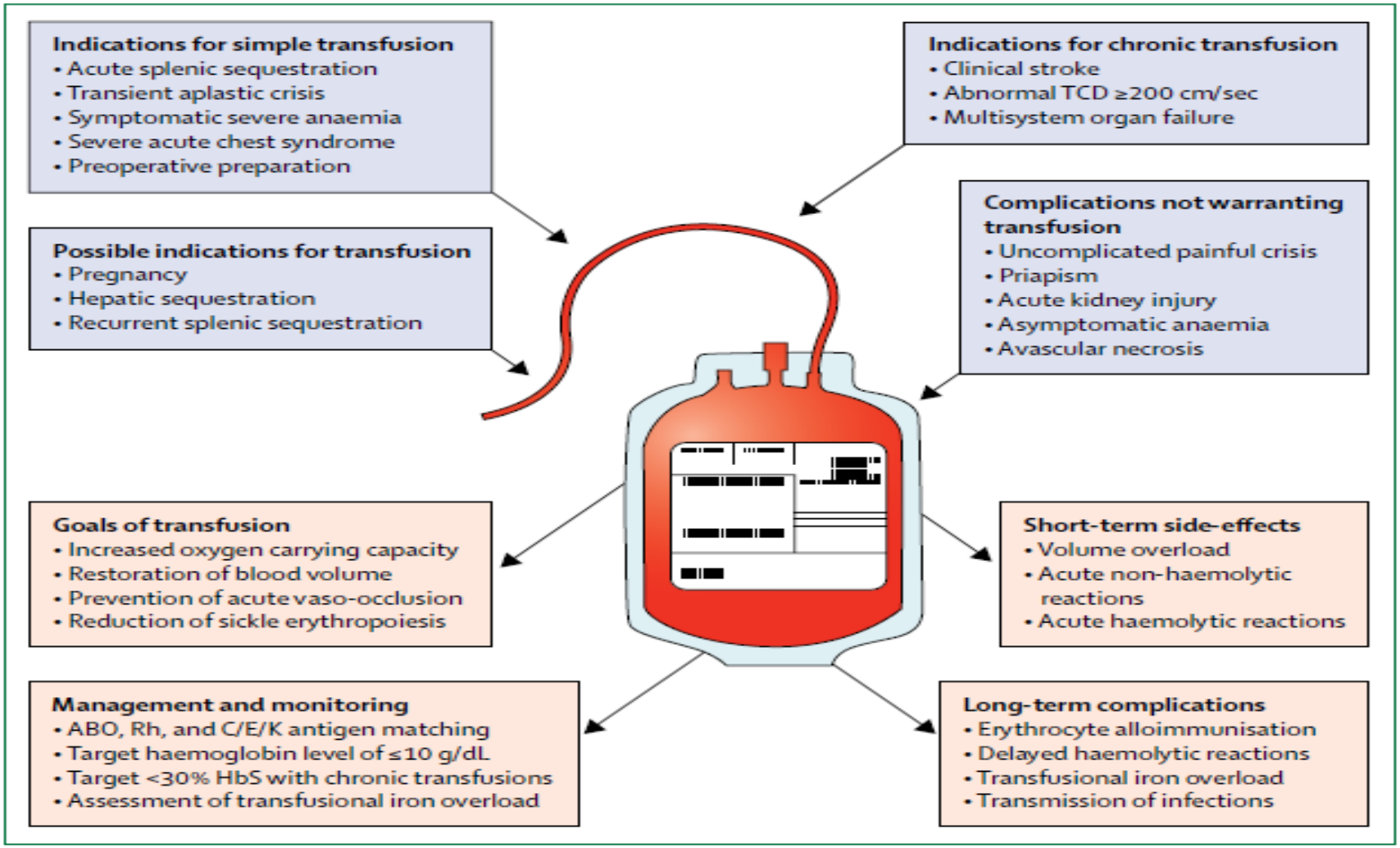

Figure 2: **Clinical indications and goals that influence the decision to transfuse a patient with sickle cell disease**
Management and monitoring, and short-term and long-term complications are described. TCD=transcranial Doppler.

Current Curative therapies/strategies

TABLE 1 | Current advances on therapy for sickle cell disease.

Changing the genotype		
(1) Allogeneic stem cell transplant	Myeloablative regimens (MAC), reduced intensity regimens (RIC), and non-myeloablative regimens (NMA)	50 clinical trials listed in ClinicalTrials.gov
(2) Autologous transplant		10 clinical trials listed in ClinicalTrials.gov
	a) Gene therapy	
	Lentiviral strategies (NCT02247843, NCT02140554, NCT02186418)	
	Inducing fetal hemoglobin	Downregulation of *BCL11A* (NCT03282656) Globin chromatin structure manipulation Downregulating beta^S globin expression
	b) Gene editing	
	Using zinc finger nucleosomes (ZFN), transcription activator-like effector nucleases (TALENs), CRISPR/Cas9 techniques (NCT03745287)	Downregulation of *BCL11A* Reactivation of HbF by HPFH mutations Globin gene repair

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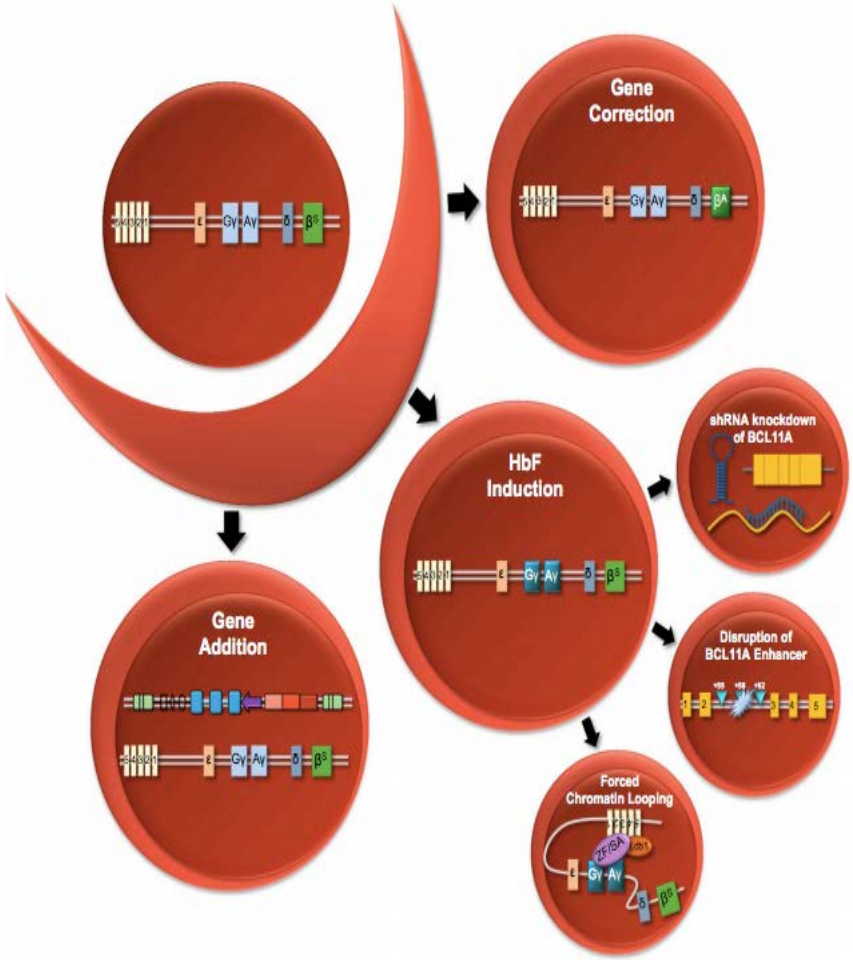
Gene therapies→ "Disease modifying" vs "curative like results":

Approaches to Gene Therapy:

(1) addition of a helpful gene(**Gene Addition)**→ the level of production of this" new hemoglobin" determines how well it changes the course of the SCD



(2) **Gene knockdown** (eg, Bcl11A) to Improve hemoglobin F levels→ level of production Fetal Hgb determines how well it changes the course of disease

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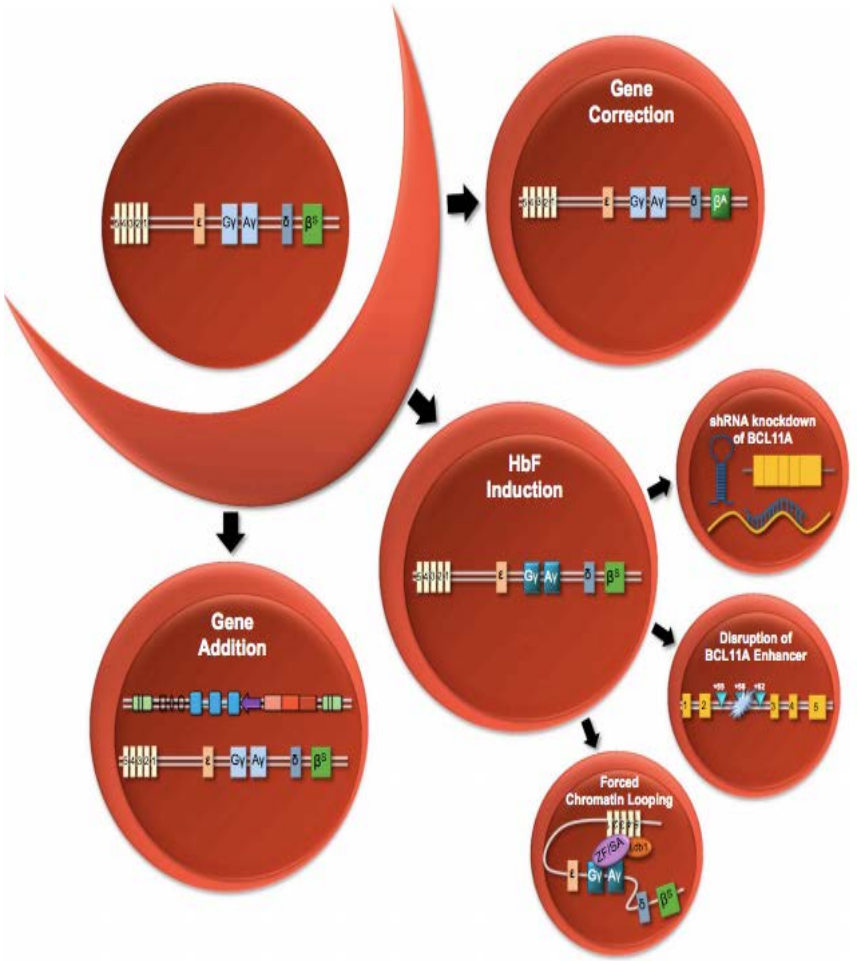
Gene therapies→ "Disease modifing" vs "curative like results":

(3) **direct globin gene editing to "correct"the mutation present** (eg, changing a hemoglobin S [HbS]–encoding gene to one encoding hemoglobin A);

(4**) Gene editing** of globin regulatory elements, to at least **partially reverse the normal hemoglobin switching from fetal to adult hemoglobin**.



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Categories of Treatment options:

Hemoglobin S polymerization	Hydroxyurea (FDA approved)	Ribonucleotide diphosphate reductase inhibitor
	LBH589/Panobinostat (NCT01245179)	Pan histone deacetylase inhibitor
	Voxelotor/GBT440 (NCT03036813) (FDA approved)	α-Globin reversible binding
	Decitabine/THU (NCT01685515)	DNMT1 inhibition
	Sanguinate (NCT02411708)	Targeting carbon monoxide delivery
Vasocclusion	IMR-687 (NCT04053803)	Phosphodiesterase 9 inhibitor
	L-Glutamine (FDA approved)	Increase NADH and NAD redox potential
	Crizanlizumab (NCT03264989) (FDA approved)	P-selectin inhibitor
	Heparinoids: Sevuparin (NCT02515838)	P-selectin and L-selectin inhibitor
	Poloxamer and Vepoloxamer	Nonionic block copolymer surfactant
Inflammation	Prasugrel, ticagrelor (NCT02482298)	P2Y2 inhibitors
	Intravenous immunoglobulin (NCT01783691)	Effects on neutrophils and monocytes activation
	Simvastatin (NCT03599609)	Vascular endothelium
	Rivaroxaban (NCT02072668)	Anti factor Xa
	N-Acetylcysteine (NCT01800526)	Oxidative stress reduction

HbF, hemoglobin F; HPFH, hereditary persistence of fetal hemoglobin; THU, tetrahydrouridine; DNMT1, DNA methyltransferase type 1.

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Indications for HSCT balanced with donor: Risk/Benefit ration Considerations availability

TABLE 2 | Indications for HSCT balanced with donor availability: Risk/benefit ratio considerations.

Matched sibling donor	Matched unrelated donor or minimally mismatched good quality cord product	Mismatched marrow donor, haploidentical donor
• Stroke • Elevated TCD velocity • Acute chest syndrome • VOC • Pulmonary Hypertension/tricuspid regurgitation jet velocity.2.5 m/s • Osteonecrosis/AVN • Red cell alloimmunization • Silent stroke specially with cognitive impairment • Recurrent priapism • Sickle nephropathy	• Stroke • Elevated TCD velocity • Recurrent acute chest syndrome despite supportive care • Recurrent severe VOC despite supportive care • Red cell alloimmunization despite intervention plus established indication for chronic transfusion therapy • Pulmonary hypertension	• Recurrent stroke despite adequate chronic transfusion therapy • Inability to tolerate supportive care though strongly indicated, e.g., red cell alloimmunization, severe VOC and inability to take hydroxyurea

HSCT, hematopoietic stem cell transplantation; AVN, avascular necrosis; TCD, transcranial doppler; VOC, vaso-occlusive crisis.

Benefits of Each Therapy

HYDROXYUREA	
Anemia/Hemolysis	↓
Vaso-occlusion	↓
Acute Chest Syndrome	↓
Stroke	?
Nephropathy	?
Pulmonary Hypertension	?
Fatigue and QoL	↓ for some patients
Mortality	↓

Benefits of Each Therapy

HYDROXYUREA	
Anemia/Hemolysis	↓
Vaso-occlusion	↓
Acute Chest Syndrome	↓
Stroke	?
Nephropathy	?
Pulmonary Hypertension	?
Fatigue and QoL	↓ for some patients
Mortality	↓

L-GLUTAMINE	
Anemia/Hemolysis	→
Vaso-occlusion	↓
Acute Chest Syndrome	↓
Stroke	No evidence
Nephropathy	No evidence
Pulmonary Hypertension	No evidence
Fatigue and QoL	→
Mortality	No evidence

Benefits of Each Therapy

HYDROXYUREA	
Anemia/Hemolysis	↓
Vaso-occlusion	↓
Acute Chest Syndrome	↓
Stroke	?
Nephropathy	?
Pulmonary Hypertension	?
Fatigue and QoL	↓ for some patients
Mortality	↓

L-GLUTAMINE	
Anemia/Hemolysis	→
Vaso-occlusion	↓
Acute Chest Syndrome	↓
Stroke	No evidence
Nephropathy	No evidence
Pulmonary Hypertension	No evidence
Fatigue and QoL	→
Mortality	No evidence

VOXELOTOR	
Anemia/Hemolysis	↓
Vaso-occlusion	→
Acute Chest Syndrome	→
Stroke	No evidence
Nephropathy	No evidence
Pulmonary Hypertension	No evidence
Fatigue and QoL	→
Mortality	No evidence

Benefits of Each Therapy

HYDROXYUREA	
Anemia/Hemolysis	↓
Vaso-occlusion	↓
Acute Chest Syndrome	↓
Stroke	?
Nephropathy	?
Pulmonary Hypertension	?
Fatigue and QoL	↓ for some patients
Mortality	↓

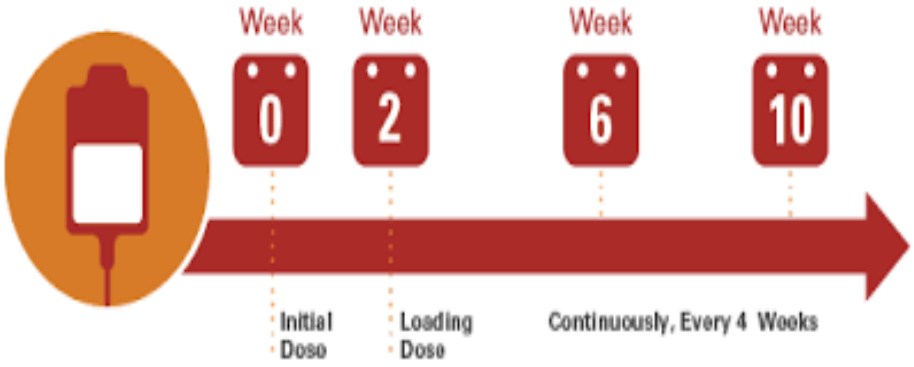
L-GLUTAMINE	
Anemia/Hemolysis	→
Vaso-occlusion	↓
Acute Chest Syndrome	↓
Stroke	No evidence
Nephropathy	No evidence
Pulmonary Hypertension	No evidence
Fatigue and QoL	→
Mortality	No evidence

VOXELOTOR	
Anemia/Hemolysis	↓
Vaso-occlusion	→
Acute Chest Syndrome	→
Stroke	No evidence
Nephropathy	No evidence
Pulmonary Hypertension	No evidence
Fatigue and QoL	→
Mortality	No evidence

CRIZANLIZUMAB	
Anemia/Hemolysis	→
Vaso-occlusion	↓
Acute Chest Syndrome	→
Stroke	No evidence
Nephropathy	No evidence
Pulmonary Hypertension	No evidence
Fatigue and QoL	→
Mortality	No evidence

ADAKVEO: Anti-stickiness/adhesion of cells to the vessell wall and to each other(Anti- P Selectin)

- Approved to decrease the frequency of vasocclusive crises in adults and childrer 16 y/o and older



- Given as an IV Infusion every 4 weeks after after initial and loading doses during Week 0 and Week 4.

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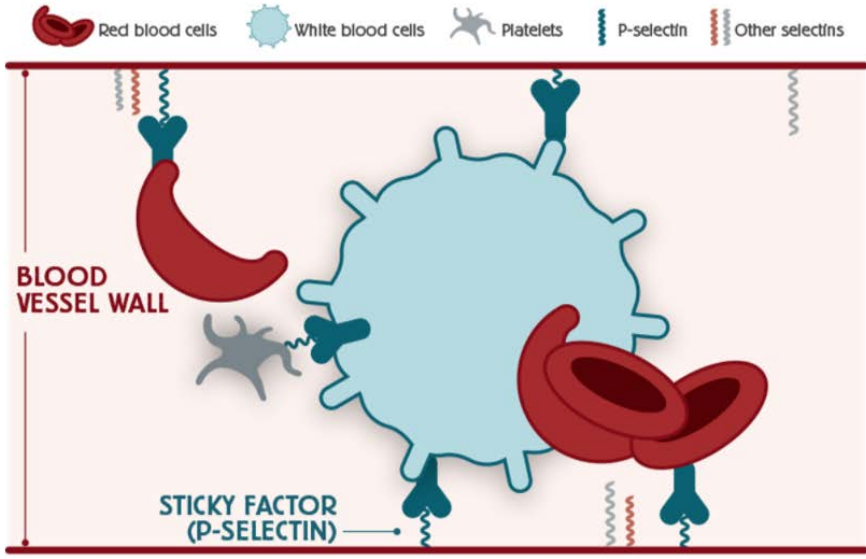
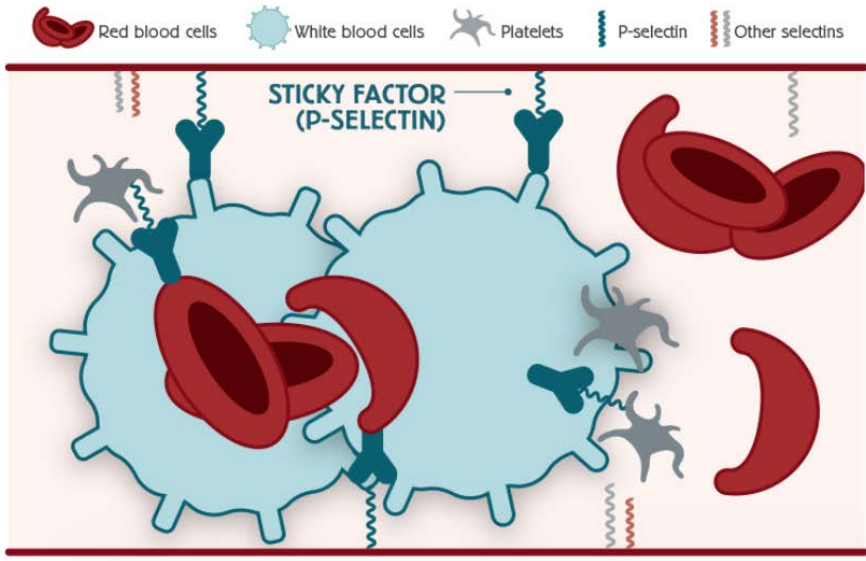
Adakveo

- **ADAKVEO attaches to P-selectin**, a sticky factor that plays a key role in blockages, also known as vaso-occlusion

- By attaching to P-selectin, **ADAKVEO blocks connections** between certain cells such as red blood cells, white blood cells, and platelets





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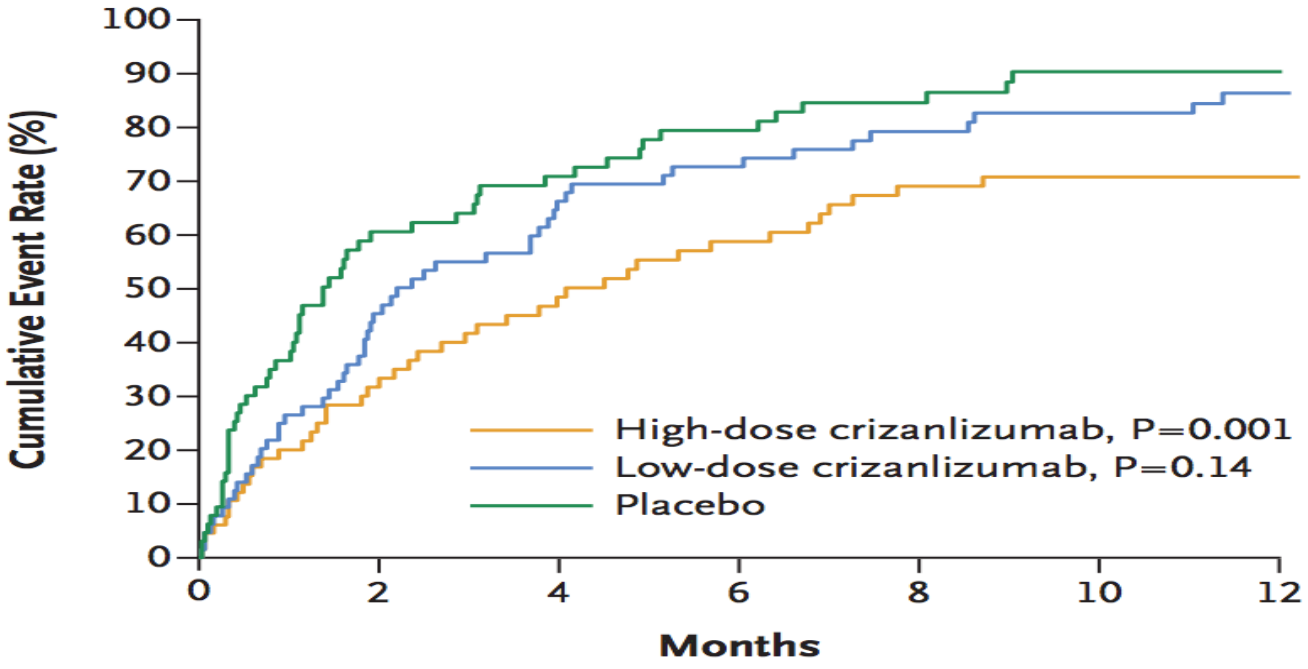
Crizanlizumab (Anti P-Selectin)

Adhesion

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

Adakveo significantly **reduced** the median annual rate of VOCs by **approximately 45% vs placebo** (**1.63 vs 2.98, respectively; *P* =.010)**. Reductions in VOC frequency were observed regardless of sickle cell disease genotype and/or hydroxyurea use.

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SICKLE CELL DISEASE

- CHRONIC, LIFELONG, DEBILITATING CONDITION RESULTING IN MULTIORGAN DYSFUNCTION AND DECREASED LIFESPAN

- BUT New Therapies are Here and more exciting ones are on the Horizon!!

Hydroxyurea

- The most effective disease modifying drug in Sickle Cell Disease in adults and children
- Offered to children 9 months and older. FDA approved for Children 2 years and older
- MSH(Adults) : HU reduced frequency of pain crisis, hospitalization, acute chest syndrome to by 50%
- Baby HUG: safety and efficacy in infants with SCA
- Common Adverse Effects: suppression of blood counts, rash, stomach discomfort;

NHLBI guidelines for SCD 2014

Charache 1995;Thornberg 2012

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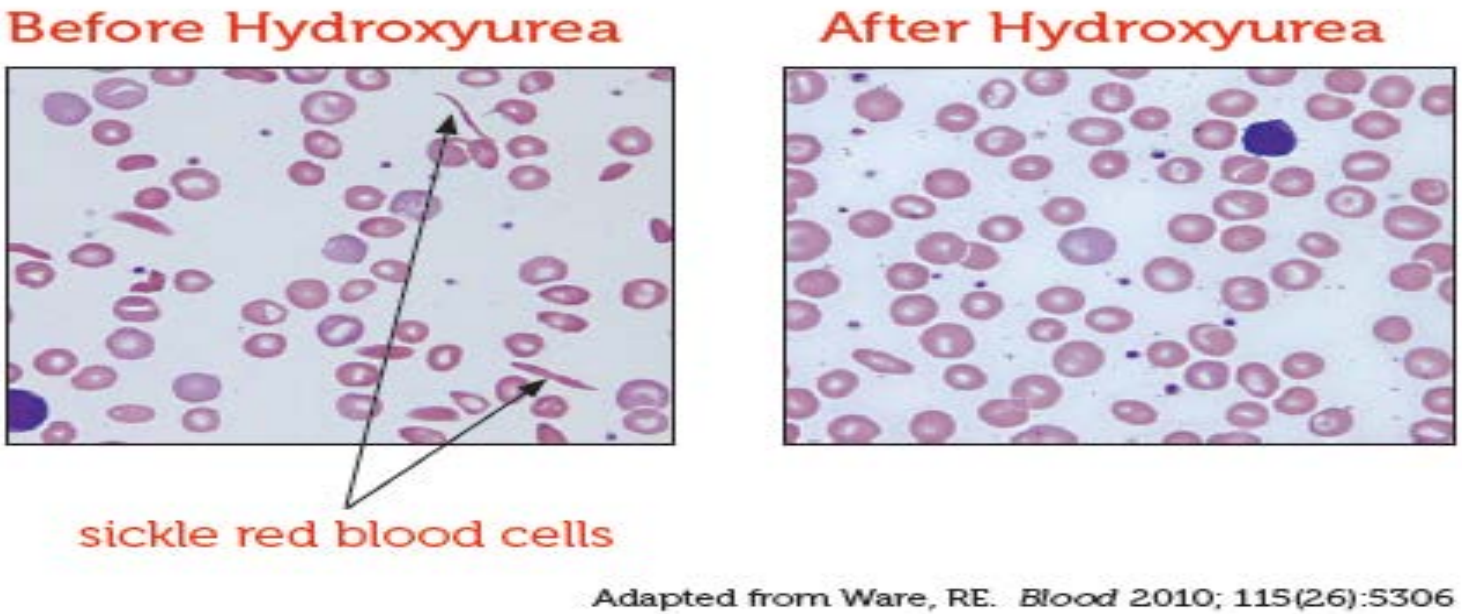
Hydroxyurea- How does it work

SEPTEMBER IS SICKLE CELL AWARENESS MONTH

Red Blood Cell Changes

How does hydroxyurea work?

Hydroxyurea makes red blood cells bigger and less likely to sickle.



Adapted from Ware, RE. *Blood* 2010; 115(26):5306

Thornburg C. et al. Effects of Hydroxyurea on pain, dactylitis, acute chest syndrome and hospitalization in sickle cell anemia (SCA): results from the baby hug trial. American Society of Pediatric Hematology Oncology Conference. May2010.

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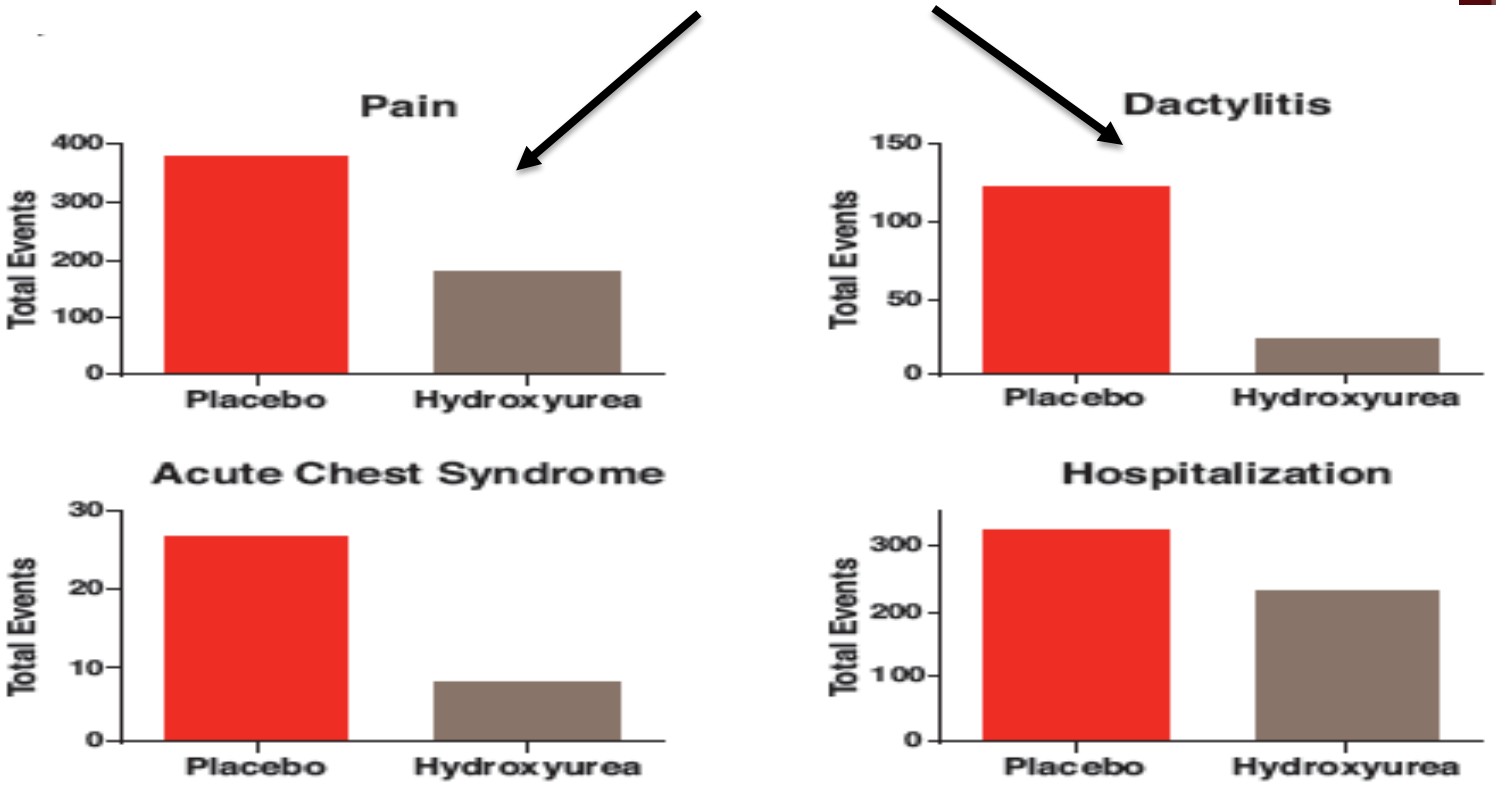
Baby HUG Study Results



Thomberg, CD et al. Impact of hydroxyurea on clinical events in the BABY HUG trial. *Blood* 2012: 120(22):4304-4310

In this study hydroxyurea did not cause any serious side effects. Children treated with hydroxyurea did not have more infections. Children treated with hydroxyurea did not have more liver or kidney problems.

Thornburg C. et al. Effects of Hydroxyurea on pain, dactylitis, acute chest syndrome and hospitalization in sickle cell anemia (SCA): results from the baby hug trial. American Society of Pediatric Hematology Oncology Conference. May2010.

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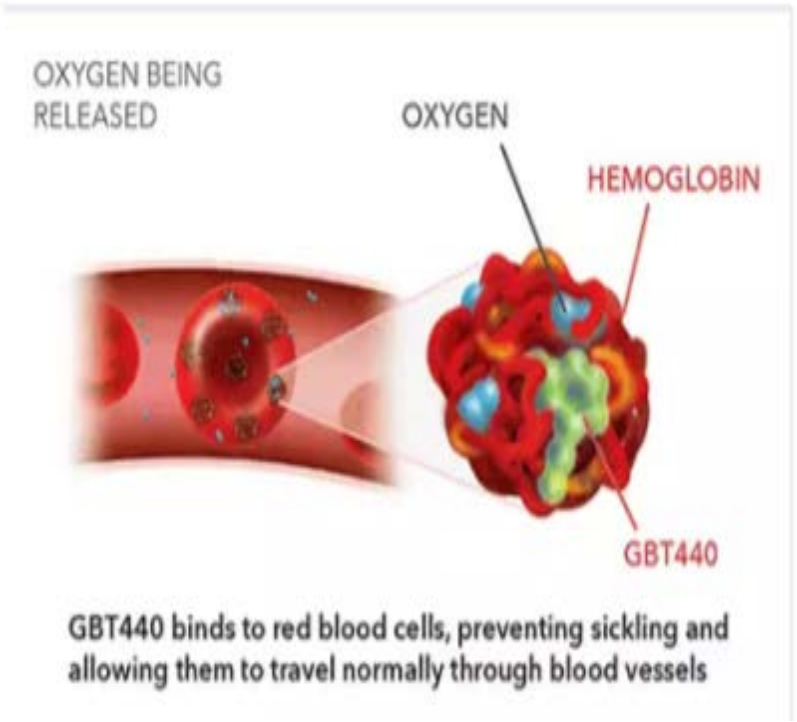
OXBRYTA(Voxelotor)

- Hemoglobin S polymerization inhibitor indicated for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older

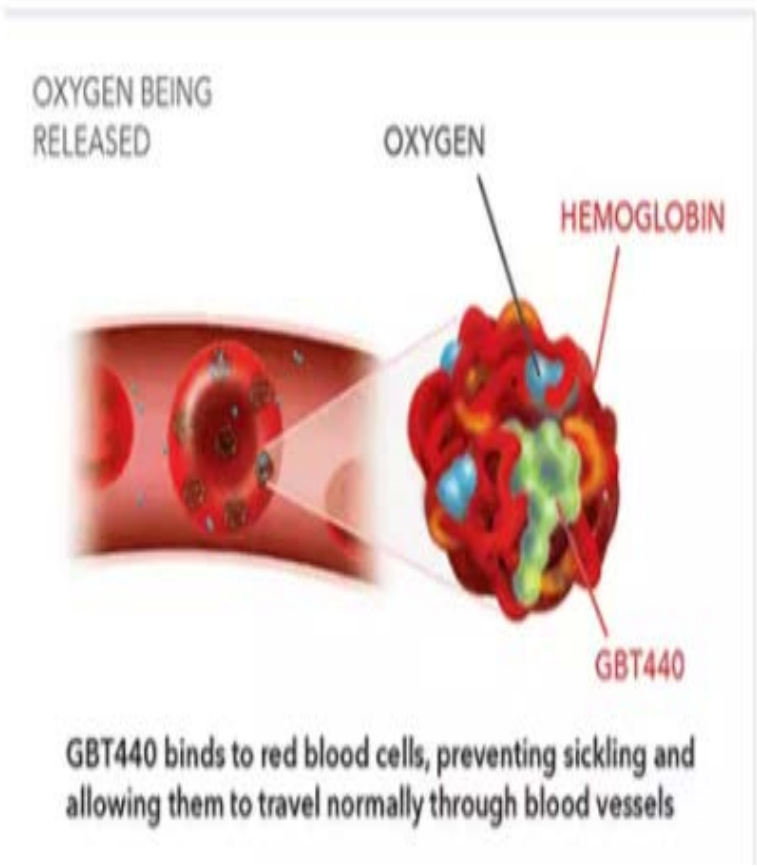


- Given once-daily(1500mg) as 500mg tablets

OXBRYTA(Voxelotor)

- Voxelotor is designed to work by ***helping hemoglobin,*** the molecules inside red blood cells, ***hold onto more oxygen as the red blood cells*** travel through the body.

- This keeps red blood cells in their normal shape and helps stop sickling.



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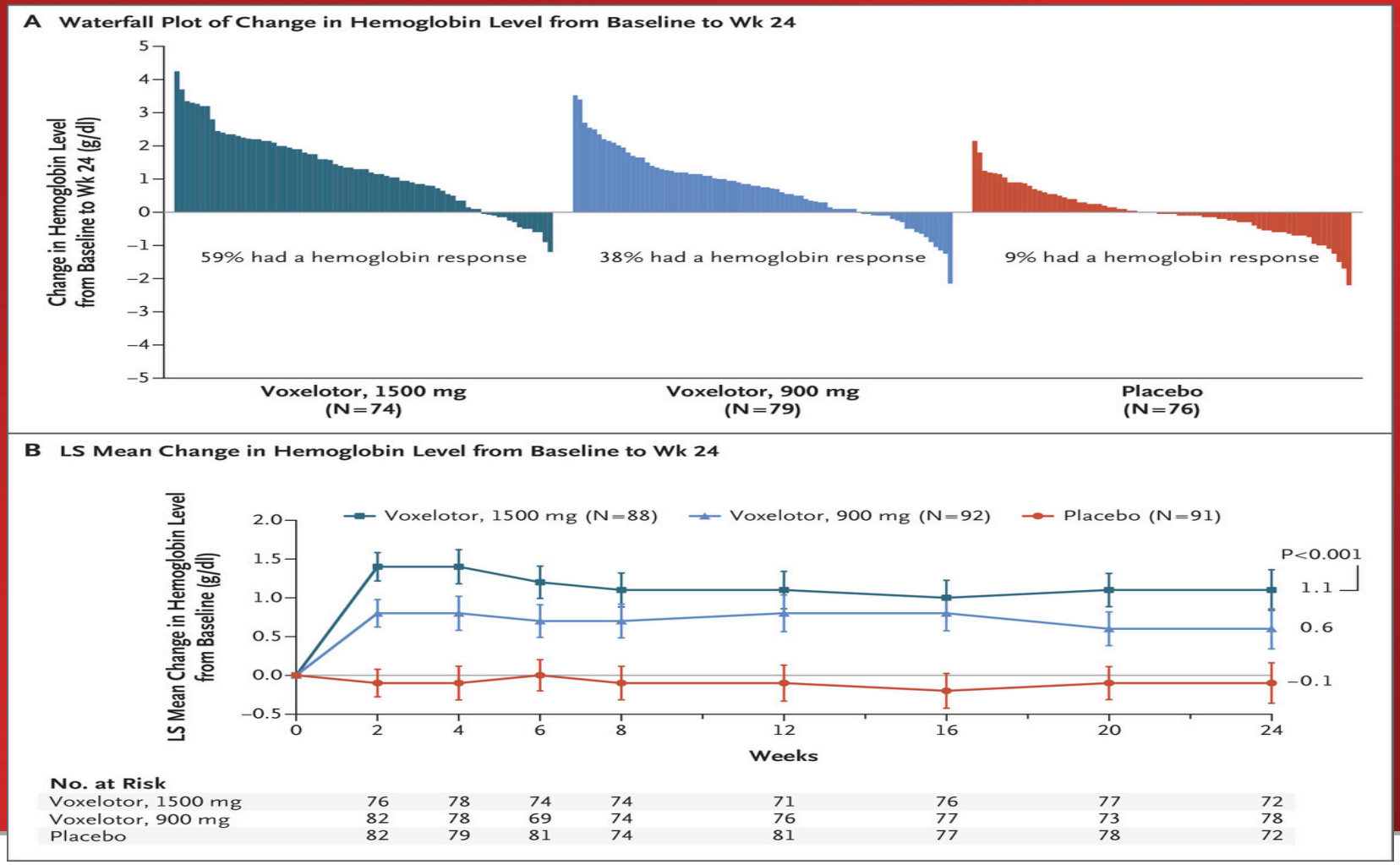
Change in Hemoglobin Level from Baseline to Week 24.



- Overall,achieving greater than 1g/dL increase in hemoglobin (51.1% vs 6.5%)
- Voxelotor increased hemoglobin levels, at 24 weeks, to a mean of 9.8 g/dL with the highest dose, and 8.9 g/dl with the lowest dose.

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Endari(L-Glutamine) :

- Essential amino acid
- Increased levels are needed in certain conditions (such as stress in the red blood cell)
- Indicated to ***reduce the acute complications of sickle cell disease*** in adult and pediatric patients 5 years of age and older
- Uptake of **L-glutamine** is several times **greater in sickle red cells** than in normal red cells primarily to increase the total intracellular NAD level

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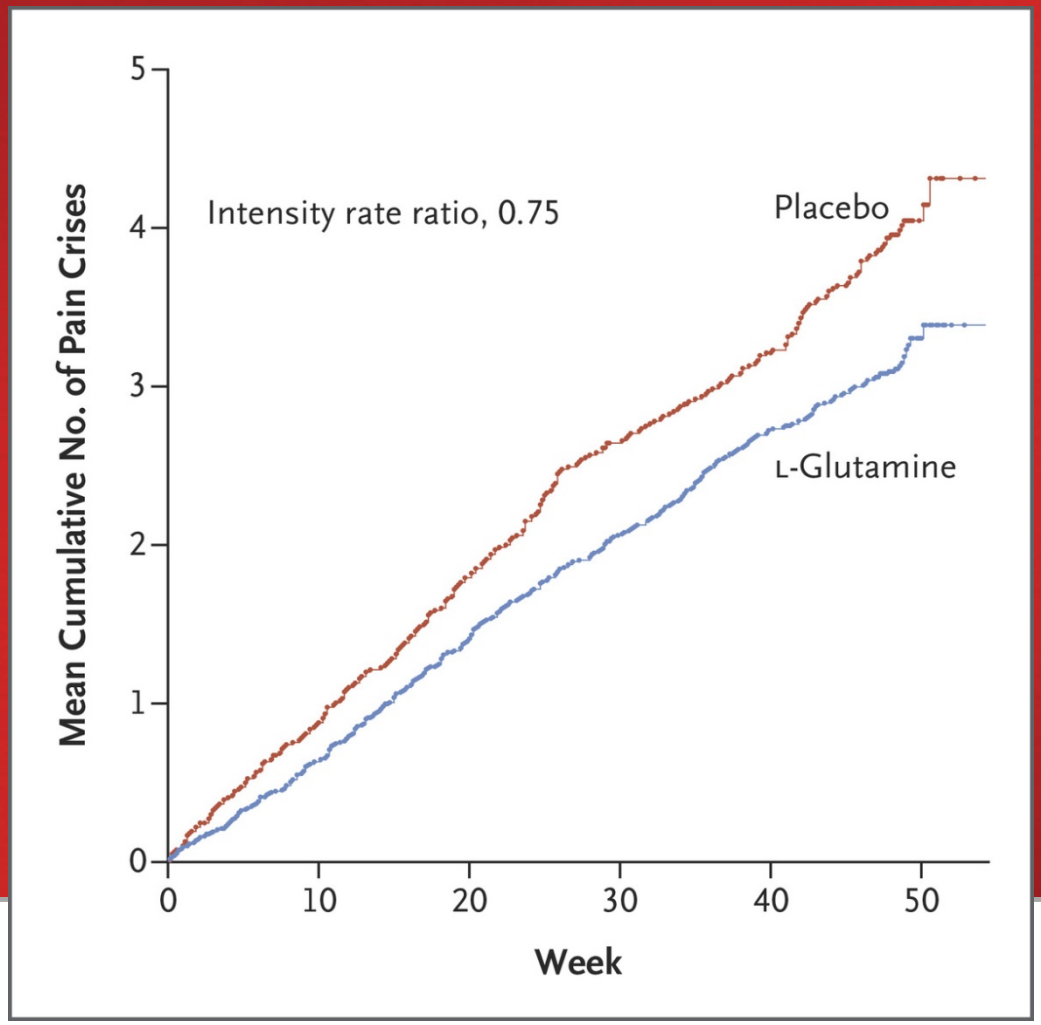
Recurrent Events of Sickle Cell–Related Pain Crisis over Time, According to Trial Group.



The cumulative number of painful crises was 25% lower in the L-glutamine group than in the placebo group over the entire 48-week treatment period

Endari(L-Glutamine) :

Endari (L-Glutamine) mechanism of action

Oxidative stress plays a major role in the pathophysiology of SCD

This stress, as manifest in a low redox ratio, makes red cells *POOR* performing (oxygen transfer, morphology, adhesiveness)

→ Poor performing red cells

Oxidants such as O_3, H_2O_2 and $O_2\bullet$ are present in all cells, but to an even greater extent in the red cells of sickle cell patients

These oxidants drive a reduction in the redox ratio and tilt the NAD^+ and NADH equilibrium toward NAD^+ (oxidized form)

→ Oxidants and NAD^+

L-Glutamine →

L-Glutamine causes cells to produce more NAD which, in effect, mops up the oxidants (essentially an anti-oxidant) – and, increases the redox ratio, prompting a whole series of red cell performance improvements

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Endari(L-Glutamine) :

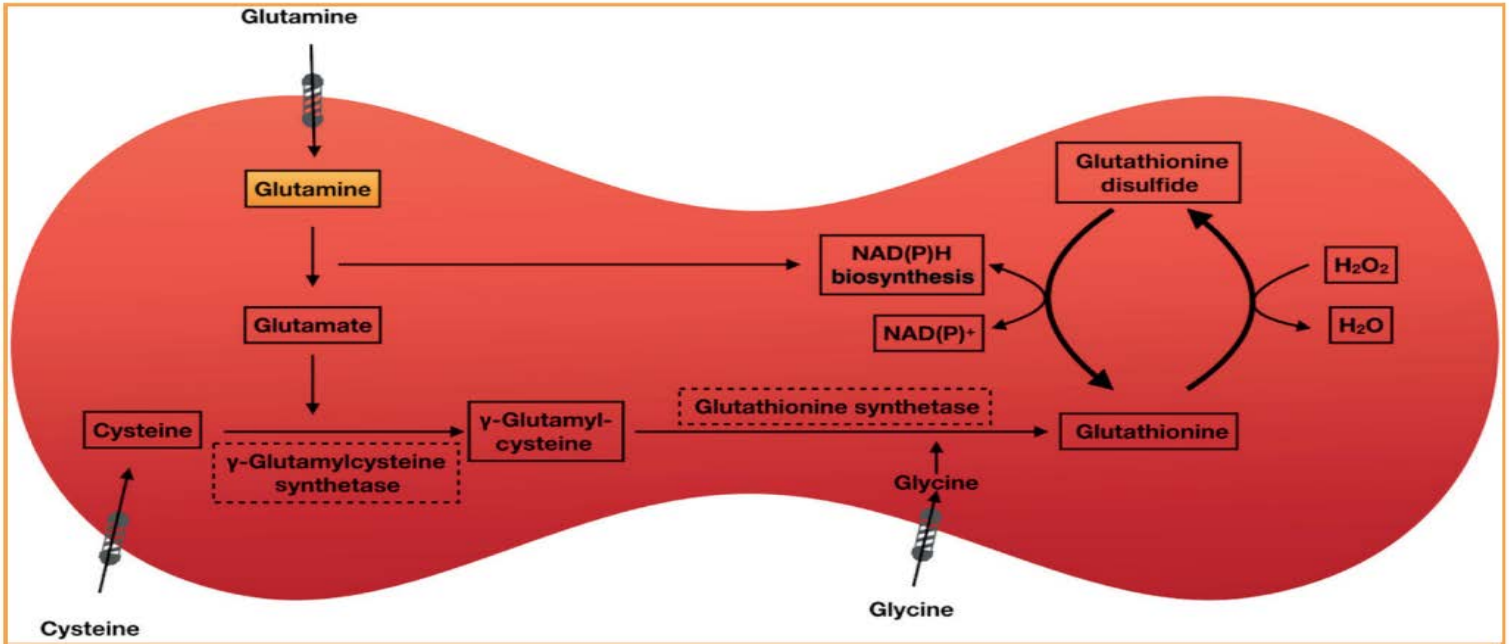

FIGURE 3. Normal glutathione metabolism. Glutathione is an antioxidant that reduces reduced nicotinamide adenine dinucleotide phosphate (NAD[P]H) in the red cell. Glutathione is synthesized from the amino acids glutamate, glycine, and, cysteine by the γ-glutamylcysteine synthetase and glutathione synthetase. In patients with sickle cell disease, glutathione and glutamine levels are low despite increased availability of glutamate, cysteine, and glycine, resulting in increased oxidant stress. L-glutamine was approved by the US Food and Drug Administration in 2017 to replenish the erythrocyte reducing potential. H_2O = water; H_2O_2 = hydrogen peroxide; NADP = nicotinamide adenine dinucleotide phosphate.

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Endari(L-Glutamine) :

- 5 grams to 15 grams orally, twice daily based on body weight.

- Each dose of Endari should be mixed in 8 oz. (240 mL) of cold or room temperature beverage or 4 oz. to 6 oz. of food before

Table 1. Recommended Dosing

Weight in kilograms	Weight in pounds	Per dose in grams	Per day in grams	Packets per dose	Packets per day
less than 30	less than 66	5	10	1	2
30 to 65	66 to 143	10	20	2	4
greater than 65	greater than 143	15	30	3	6

CASE

16 y/o male with Hgb SS Sickle cell disease who is maintained on hydroxyurea @ 25mg/kg/day with Hgb 8.5 and fetal hemoglobin(Hgb F) of 25% (MCV 100) and has had an increase in pain in his lower legs x 6 mos. What should we do to optimize his sickle cell care?

What are his treatment options??

Oxbryta(Voxelotor)?

Adakveo(Crizanlizumab)?

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SICKLE CELL DISEASE: Exciting times are here!

- SCD: Chronic, lifelong, debilitating condition resulting in multiorgan dysfunction and decreased lifespan

- BUT New Therapies are Here and are on the Horizon!!

- Discuss with your Hematology provider!

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