MAYO CLINIC

Sickle Me Pink: Promising Advances in Sickle Cell Disease Management

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Pharmacy Grand Rounds
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Learning Objectives

- Describe the pathophysiology and complications associated with sickle cell disease
- Review standard treatment modalities of sickle cell disease
- Discuss recent literature regarding advancements in sickle cell disease therapy

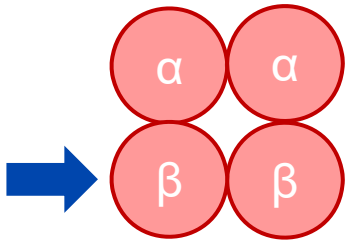
Sickle Cell Disease Overview

- Autosomal recessive genetic condition
  - Most common inherited blood disorder in the United States
    - ~100,000 Americans have SCD
  - Improved long-term survival rates since mandated newborn screening
  - Symptoms appear around 5-6 months of age
    - Acute pain, fatigue, and jaundice
- Affects millions of people throughout the world
  - Primarily African descent
    - 1 in 13 African-American newborns will have SCT
  - Also prevalent among Hispanic, southern European, Mediterranean, Native American, Middle Eastern, and Asian Indian background

Centers for Disease Control and Prevention (2020).
National Heart Lung and Blood Institute (2014).

SCD: Sickle cell disease
SCT: Sickle cell trait

Nomenclature



Sickle Cell Disorder	•Sickle HbS gene mutation on at least 1 β-globin gene
Sickle Cell Trait	•1 normal Hb "A" gene + 1 HbS gene mutation •Benign carrier (HbAS)
Sickle Cell Disease	•HbS + 2nd β-globin gene mutation •Mild form: HbSC •Rare forms: HbSD, HbSE, HbSO
Sickle Cell Anemia	•Type of SCD •Presence of 2 sickle cell genes (HbSS)
Sickle β-Thalassemia	•Another inherited blood disorder affecting Hb •β^0 = severe disease (looks like HbSS) •β^+ = mild disease

Centers for Disease Control and Prevention (2020).
National Heart Lung and Blood Institute (2014).
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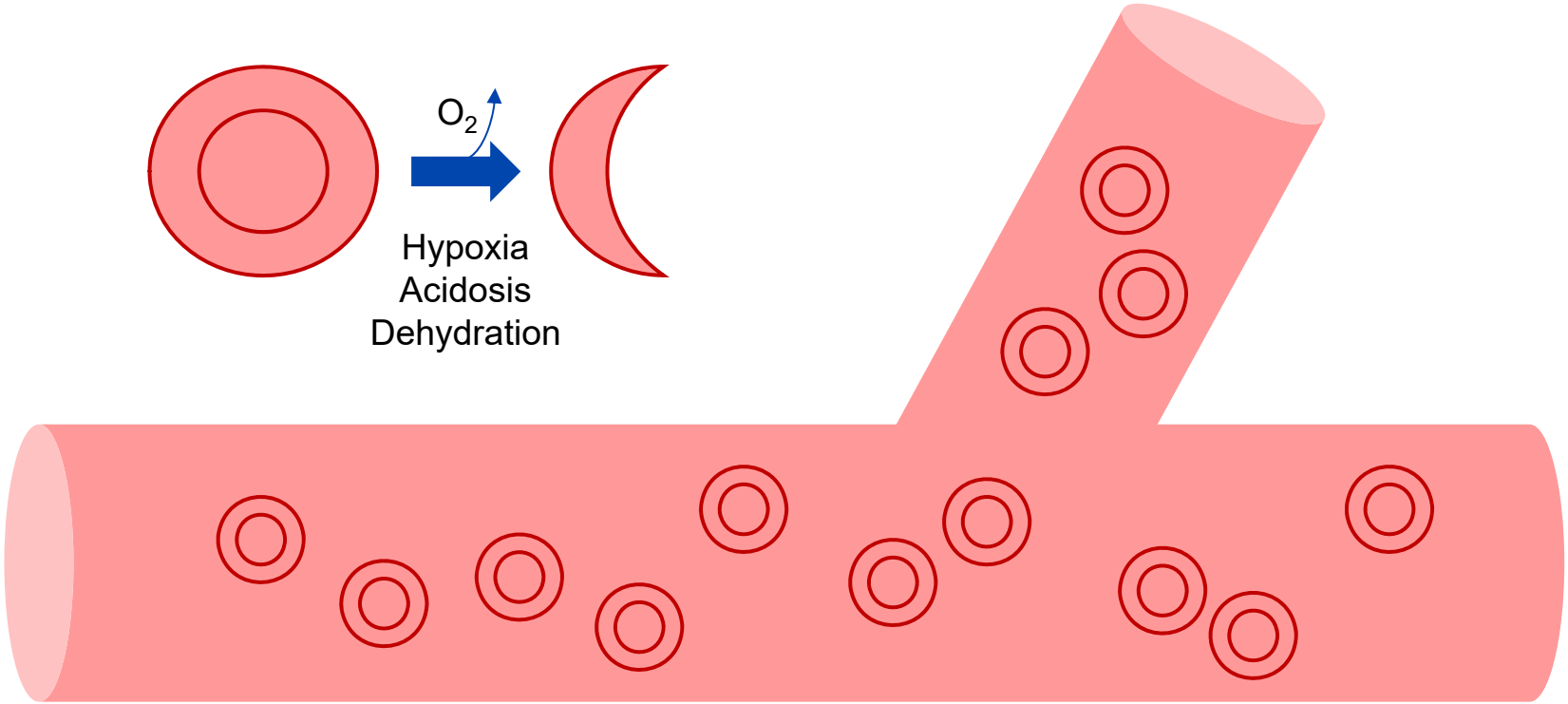
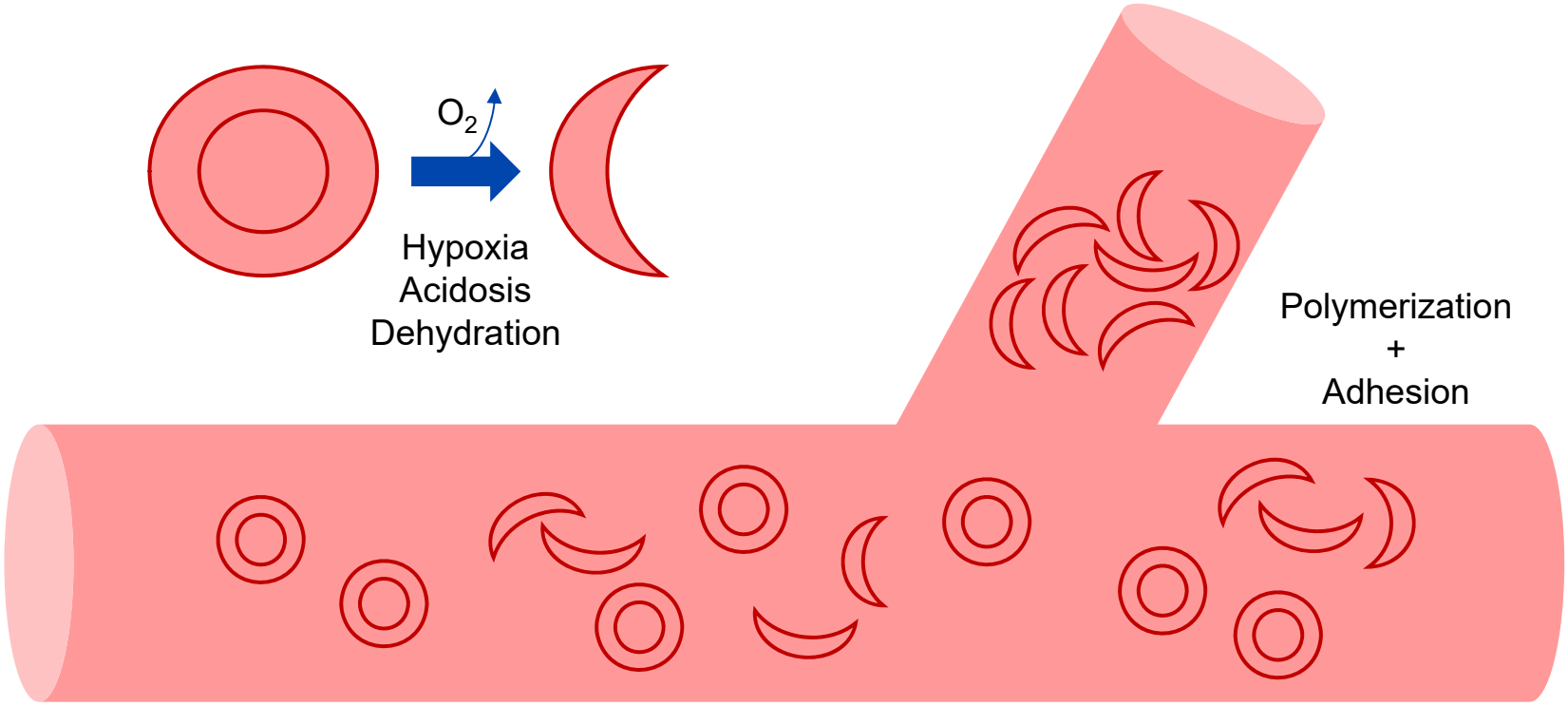
Pathophysiology



National Heart Lung and Blood Institute (2014).
Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.

Pathophysiology



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Disease Complications

Acute

- Fever and infection
- Vaso-occlusion (acute pain crisis)
  - Dactylitis
  - Acute chest syndrome
  - Cerebrovascular accident
  - Priapism
- Splenic sequestration
- Aplastic crisis

Chronic

- Anemia
  - Iron overload
- Dysfunctional spleen
- Multi-system organ damage
  - Renal disease
  - Heart failure
  - Pulmonary hypertension
  - Retinopathy
  - Skin ulcers
  - Avascular necrosis

Centers for Disease Control and Prevention (2020).
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Acute Pain Crisis

- Deep, throbbing pain widespread throughout body
- Most common reason for ED visits and hospitalizations
  - Assumptions about drug-seeking behavior due to need for opioid medications
  - Can lead to chronic pain
- Management considerations
  - Treat underlying precipitating factors
  - Maintain adequate hydration
  - Avoid delays in analgesia
    - Analgesic choice dependent on history of response, patterns of use, current status (pain scales), and other medical conditions

National Heart Lung and Blood Institute (2014).
Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.

Pain Management

Non-Opioid	Opioid	Adjuvant
• Acetaminophen • Ibuprofen • Ketorolac	• Oxycodone • Hydromorphone • Morphine • Fentanyl	• Ketamine • Gabapentin • SSRIs • SNRIs

IV or PCA

National Heart Lung and Blood Institute (2014).
Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.

Learning Objective Question #1

- Which of the following would be classified as the most severe form of sickle cell?
  A. HbAS
  B. HbSβ^0
  C. HbSβ^+
  D. HbSC

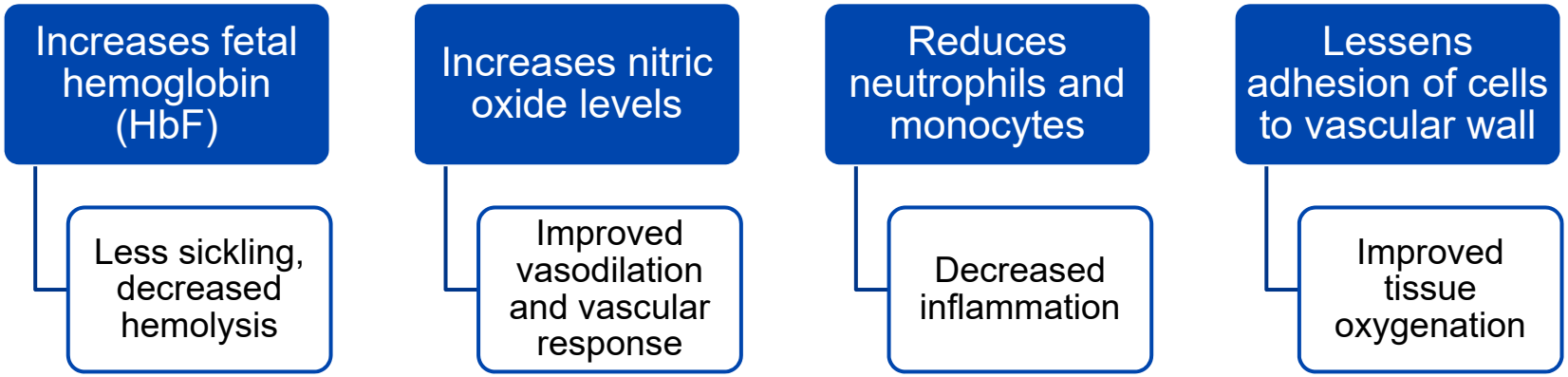
Chronic Health Maintenance

- Hydroxyurea
- Allogeneic Stem Cell Transplant
- RBC Transfusions
- Infection Prevention

National Heart Lung and Blood Institute (2014).
Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.

Hydroxyurea

- FDA approval in 1998
- Reduces and prevents many SCD complications



Wang et al. (2011). *Lancet*. 377(9779):1663:1672.
Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.

Hydroxyurea

- Limited safety and efficacy data in pediatrics
  - ≥ 9 months and older
- Initial: 20 mg/kg/day
  - Dose increases every 8 weeks by 5 mg/kg/day
  - Maximum dose: 2,500 mg daily (35 mg/kg/day)
- Toxicity → Stop therapy when:
  - ANC < 1,500-3,000/mcL
  - Plt < 80k/mcL
    - Reinitiate at 5 mg/kg/day lower than dose prior to myelosuppressive effects

Wang et al. (2011). *Lancet*. 377(9779):1663:1672.
Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.

Hydroxyurea

Pros

- Decreases complications
- Reduces ED visits and hospitalizations
- Improves quality of life and overall survival

Cons

- Compliance
- No secondary stroke prevention
- Hazardous medication
- Bone marrow suppression

Wang et al. (2011). *Lancet*. 377(9779):1663:1672.
Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.

Hematopoietic Stem Cell Transplant

- Only therapy that can cure SCD
- Overall survival with sibling-match donors ~95%
  - Increased mortality without HLA match

Optimal Candidate	Risks
• < 16 years • Severe SCD • Disease complications • HLA-compatible full sibling	• GVHD • HLA-mismatched donor • Secondary malignancies

National Heart Lung and Blood Institute (2014).
Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.

GVHD: Graft vs. host disease
HLA: Human leukocyte antigen
SCD: Sickle cell disease

Chronic RBC Transfusions

- Dilutes amount of sickled RBCs with healthy RBCs
  - Lessens hemolysis → corrects anemia
- Administered every 3-4 weeks
  - Adjusted to maintain [HbS] < 30% total Hb

Risks

- Blood hyperviscosity
- Volume overload
- Iron depositions in organs (heart, liver)

Iron Chelation Therapy

- Deferoxamine (IV/SQ)
- Deferasirox (PO)
- Deferiprone (PO)

National Heart Lung and Blood Institute (2014).
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Infection: Dysfunctional Spleen

- Major cause of morbidity and mortality
  - Sepsis and meningitis
    - *S. pneumoniae, H. influenza,* and *N. meningitidis*
    - *M. pneumoniae*
- Other infectious concerns
  - Viruses (pneumonia)
  - *Salmonella* spp. (osteomyelitis)
- Infection prophylaxis
  - Immunizations → Pneumococcal and meningococcal
  - Penicillin

National Heart Lung and Blood Institute (2014).
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Infection Prevention: Penicillin Prophylaxis

Who?
- All infants with HbSS and HbSβ-thalassemia

What?
- < 3 years: Penicillin V potassium 125 mg PO BID
- ≥ 3 years: Penicillin V potassium 250 mg PO BID

When?
- Start at 2 months old
- Continue until 5 years old

Why?
- Decrease infections and risk of death

National Heart Lung and Blood Institute (2014).
Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.

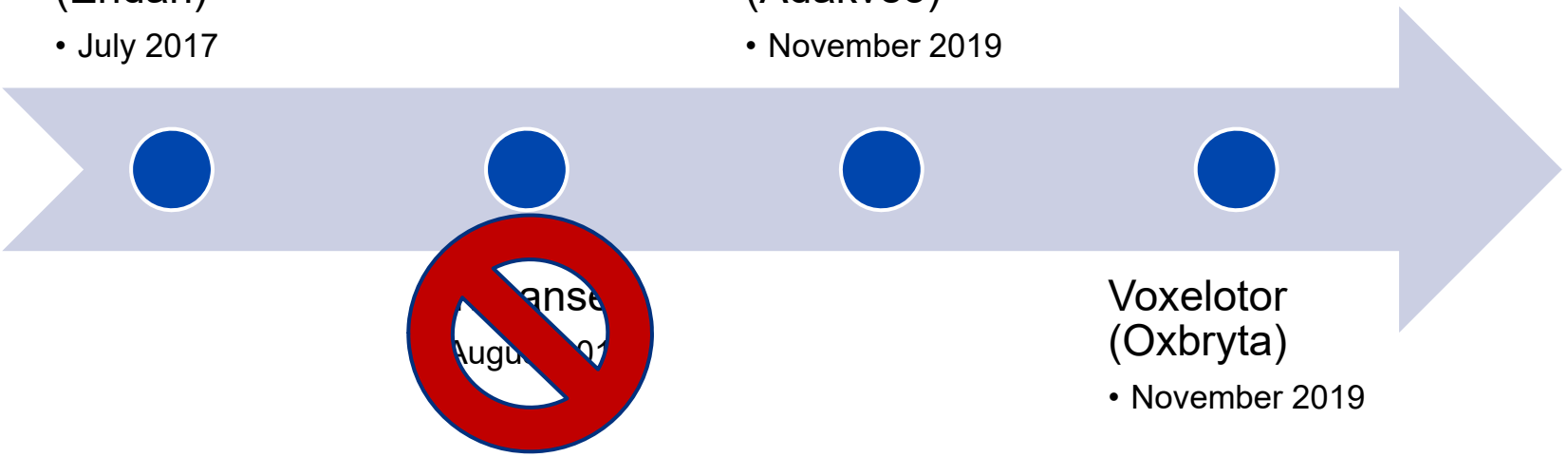
Learning Objective Question #2

- 4 yo F has been diagnosed with HbSS SCD. What is an appropriate initial therapy regimen?
  A. Hydroxyurea 20 mg/kg/day
  B. Hydroxyurea 20 mg/kg/day + PCN 125 mg BID
  C. Hydroxyurea 35 mg/kg/day + PCN 125 mg BID
  D. Hydroxyurea 20 mg/kg/day + PCN 250 mg BID

New Therapy Options

L-Glutamine (Endari)
- July 2017

Crizanlizumab (Adakveo)
- November 2019



Voxelotor (Oxbryta)
- November 2019

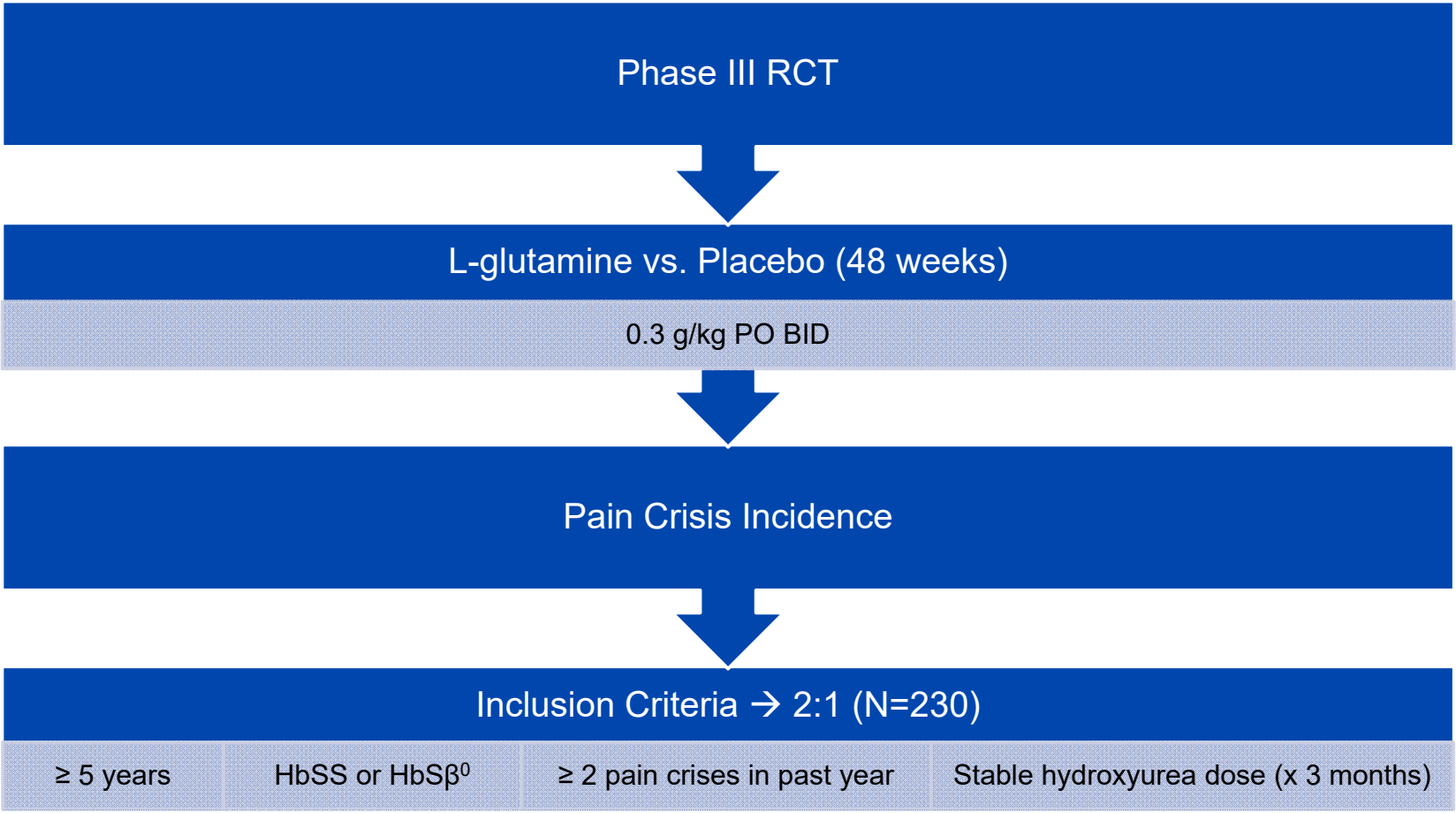
Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.
Niihara et al. (2018). *N Engl J Med*. 379(3):226-235.
ClinicalTrials.gov (2019). NCT02187003.
Ataga et al. (2017). *N Engl J Med*. 376(5):429-439.
Vichinsky et al. (2019). *N Engl J Med*. 381(6):509-519.

L-Glutamine

- Anti-inflammatory amino acid
  - Regulates and prevents oxidative damage to RBCs
- Dosing:
  - < 30 kg: 5 g (1 packet) BID
  - 30-65 kg: 10 g (2 packets) BID
  - > 65 kg: 15 g (3 packets) BID
- Adverse effects:
  - Nausea, constipation, headache, and arthralgia
- Monitoring:
  - Renal and hepatic function → no suggested dose adjustments

Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.
Niihara et al. (2018). *N Engl J Med*. 379(3):226-235.

Niihara et al. (2018)



Niihara et al. (2018). *N Engl J Med*. 379(3):226-235.

Baseline Characteristics

Characteristic, N (%)	L-Glutamine (N=152)	Placebo (N=78)
5-12 years	34 (22.4)	17 (21.8)
13-18 years	41 (27)	26 (33.3)
> 18 years	77 (50.7)	35 (44.9)
Hydroxyurea use	101 (66.4)	52 (66.7)
0-1 pain crisis	1 (0.7)	1 (1.3)
2-5 pain crises	128 (84.2)	61 (78.2)
6-9 pain crises	15 (9.9)	14 (17.9)
≥ 10 pain crises	8 (5.3)	2 (2.6)

Niihara et al. (2018). *N Engl J Med*. 379(3):226-235.

Primary Outcome

End Point	L-Glutamine	Placebo	P-value
Median number of pain crisis (mean ± SD)	3.2 ± 2.24	3.9 ± 2.54	0.005

Niihara et al. (2018). *N Engl J Med*. 379(3):226-235.

Secondary Outcomes

End Point	L-Glutamine (N=152)	Placebo (N=78)	P-value
Hospitalizations for pain crises (mean ± SD)	2.3 ± 1.99	3 ± 2.33	0.005
ED visits for pain (mean ± SD)	1.1 ± 1.49	1.5 ± 2.29	0.09
Cumulative days in hospital (mean ± SD)	12.1 ± 16.6	18.1 ± 27.4	0.02
Median time to first pain crisis (days)	84 (95% CI 62-109)	54 (95% CI 31-73)	0.02
Median time to second pain crisis (days)	212 (95% CI 153-250)	133 (95% CI 115-179)	0.03
≥ 1 acute chest syndrome episode (%)	13 (8.6)	18 (23.1)	0.003

Niihara et al. (2018). *N Engl J Med*. 379(3):226-235.

Safety Analysis

Adverse Event, N (%)	L-Glutamine (N=151)	Placebo (N=78)
Tachycardia	8 (5.3)	4 (5.1)
Constipation	38 (25.2)	19 (24.4)
Nausea	34 (22.5)	13 (16.7)
Vomiting	22 (14.6)	10 (12.8)
Upper abdominal pain	16 (10.6)	6 (7.7)
Diarrhea	12 (7.9)	5 (6.4)
Chest pain (non-cardiac)	21 (13.9)	7 (9.0)
Fatigue	9 (6.0)	1 (1.3)
Urinary tract infection	10 (6.6)	3 (3.8)
Extremity pain	24 (15.9)	6 (7.7)
Back pain	20 (13.2)	5 (6.4)
Headache	32 (21.2)	14 (17.9)
Dizziness	8 (5.3)	4 (5.1)
Nasal congestion	11 (7.3)	5 (6.4)

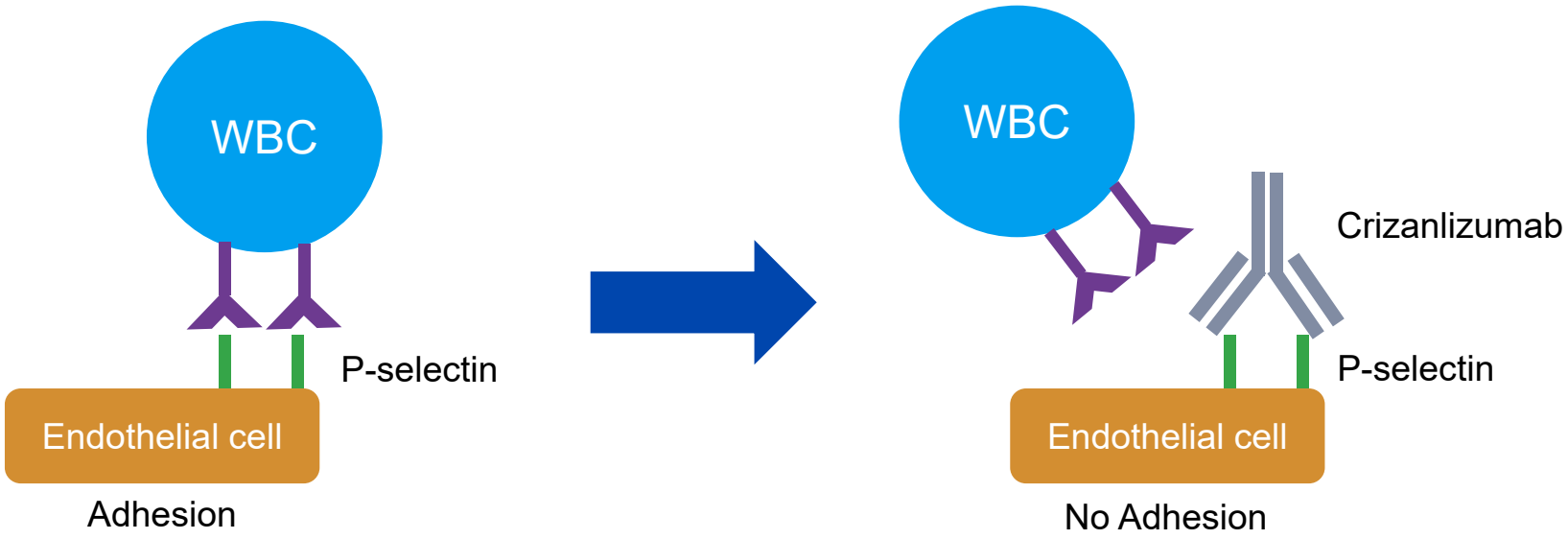
Niihara et al. (2018). *N Engl J Med*. 379(3):226-235.

Crizanlizumab

- Anti-adhesion monoclonal antibody
  - Helps maintain normal blood flow of WBCs by binding to P-selectin to stop vaso-occlusion
- Dosing: ≥ 16 years
  - Week 0 and 2: 5 mg/kg IV over 30 minutes
  - Subsequent doses: 5 mg/kg every 4 weeks
- Adverse effects:
  - Nausea, arthralgia, and back pain
- Monitoring:
  - Infusion-related reactions

Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.
Ataga et al. (2017). *N Engl J Med*. 376(5):429-439.

Mechanism of Action



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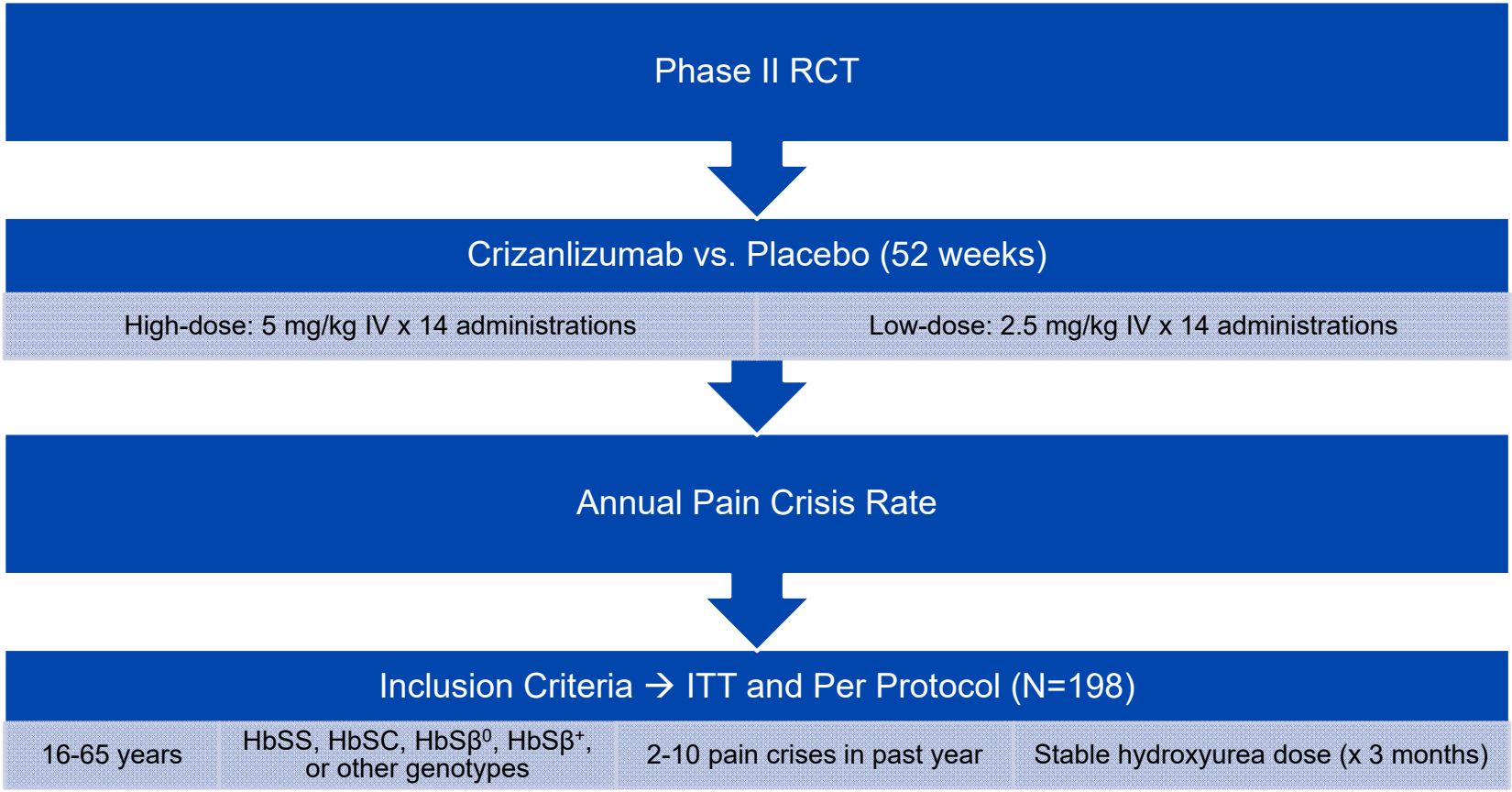
SUSTAIN Trial (2017)



Ataga et al. (2017). *N Engl J Med*. 376(5):429-439.

Mayo Clinic Children's Center

ITT: Intention to treat

Baseline Characteristics

Characteristic	High-Dose (N=67)	Low-Dose (N=66)	Placebo (N=65)
Age (yrs), median (range)	29 (16-63)	29 (17-57)	26 (16-56)
HbSS, N (%)	47 (70)	47 (71)	47 (72)
HbSC, N (%)	9 (13)	15 (23)	8 (12)
HbSβ^0, N (%)	3 (4)	2 (3)	1 (2)
HbSβ^+, N (%)	7 (10)	2 (3)	1 (2)
Other genotype, N (%)	1 (1)	0	2 (3)
Hydroxyurea use, N (%)	42 (63)	41 (62)	40 (62)
2-4 pain crisis, N (%)	42 (63)	41 (62)	41 (63)
5-10 pain crisis, N (%)	25 (37)	25 (38)	24 (37)

Ataga et al. (2017). *N Engl J Med*. 376(5):429-439.

Primary Outcome

ITT End Point	High-Dose (N=67)	Low-Dose (N=66)	Placebo (N=65)
Median crisis rate per year (IQR)	1.63 (0-3.97)	2.01 (1-3.98)	2.98 (1.25-5.87)
P-value	0.01	0.18	---
Patients with crisis rate of 0 at end of trial (N)	24	12	11

Per Protocol End Point	High-Dose (N=40)	Low-Dose (N=44)	Placebo (N=41)
Median crisis rate per year (IQR)	1.04 (0-3.42)	2 (1-3.02)	2.18 (1.96-4.96)
P-value	0.02	0.13	---
Patients with crisis rate of 0 at end of trial (N)	15	7	5

Ataga et al. (2017). *N Engl J Med*. 376(5):429-439.

ITT: Intention to treat

Secondary Outcomes

End Point	High-Dose (N=67)	Low-Dose (N=66)	Placebo (N=65)
Median rate of days hospitalized per year (IQR)	4 (0-25.72)	6.87 (0-18)	6.87 (0-28.3)
P-value	0.45	0.85	---
Median time to 1st crisis, months (IQR)	4.07 (1.31-NR)	2.2 (0.95-6.6)	1.38 (0.39-4.9)
Hazard ratio (95% CI)	0.5 (0.33-0.74)	0.75 (0.52-1.1)	---
P-value	0.001	0.14	---
Median time to 2nd crisis, months (IQR)	10.32 (4.47-NR)	9.2 (3.94-12.16)	5.09 (2.96-11.01)
Hazard ratio (95% CI)	0.53 (0.33-0.87)	0.69 (0.44-1.09)	---
P-value	0.02	0.1	---

Ataga et al. (2017). *N Engl J Med*. 376(5):429-439.

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NR: Not reportable

Safety Analysis

- Adverse events
  - Headache, back pain, nausea, arthralgia, UTI
- Serious adverse events
  - Pyrexia, influenza, pneumonia

Variable	High-Dose (N=66)	Low-Dose (N=64)	Placebo (N=62)
≥ 1 serious adverse event, N (%)	17 (26)	21 (33)	17 (27)
≥ 1 adverse event, N (%)	57 (86)	56 (88)	55 (89)

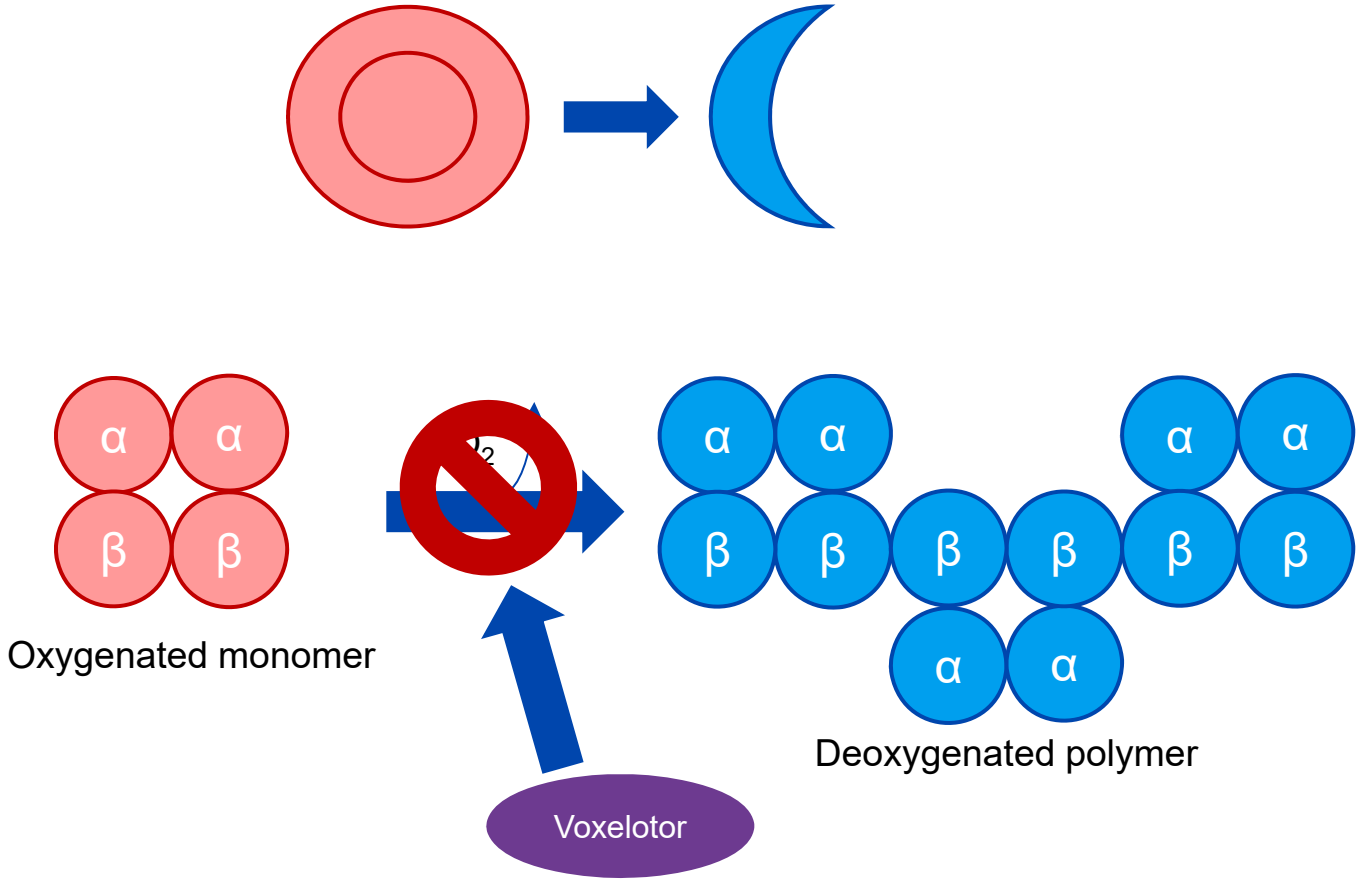
Ataga et al. (2017). *N Engl J Med*. 376(5):429-439.

Voxelotor

- Anti-sickling agent → Regulates hemoglobin affinity for oxygen which inhibits hemoglobin polymerization
  - Decreases concentration of deoxygenated sickle hemoglobin
- Dosing: ≥ 12 years
  - 1,500 mg PO daily
  - Dose adjustments:
    - Hepatic impairment, CYP3A4 inducers and inhibitors
- Adverse effects:
  - Headache, diarrhea, abdominal pain, nausea, and rash
- Monitoring:
  - Hb levels, hepatic function, and hypersensitivity reactions

Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.
Vichinsky et al. (2019). *N Engl J Med*. 381(6):509-519.

Mechanism of Action



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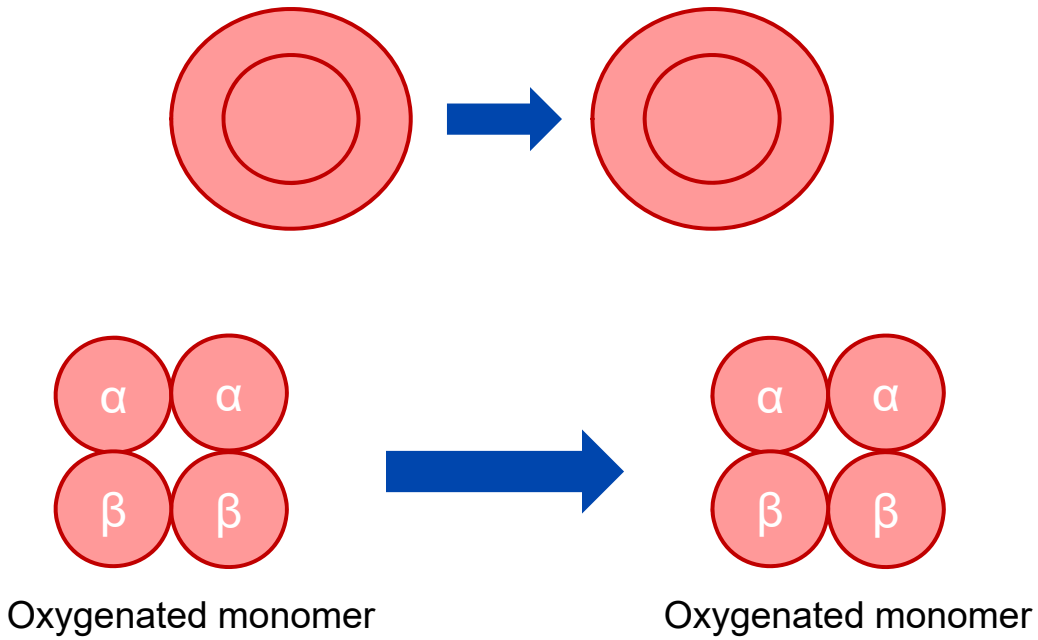
Mechanism of Action



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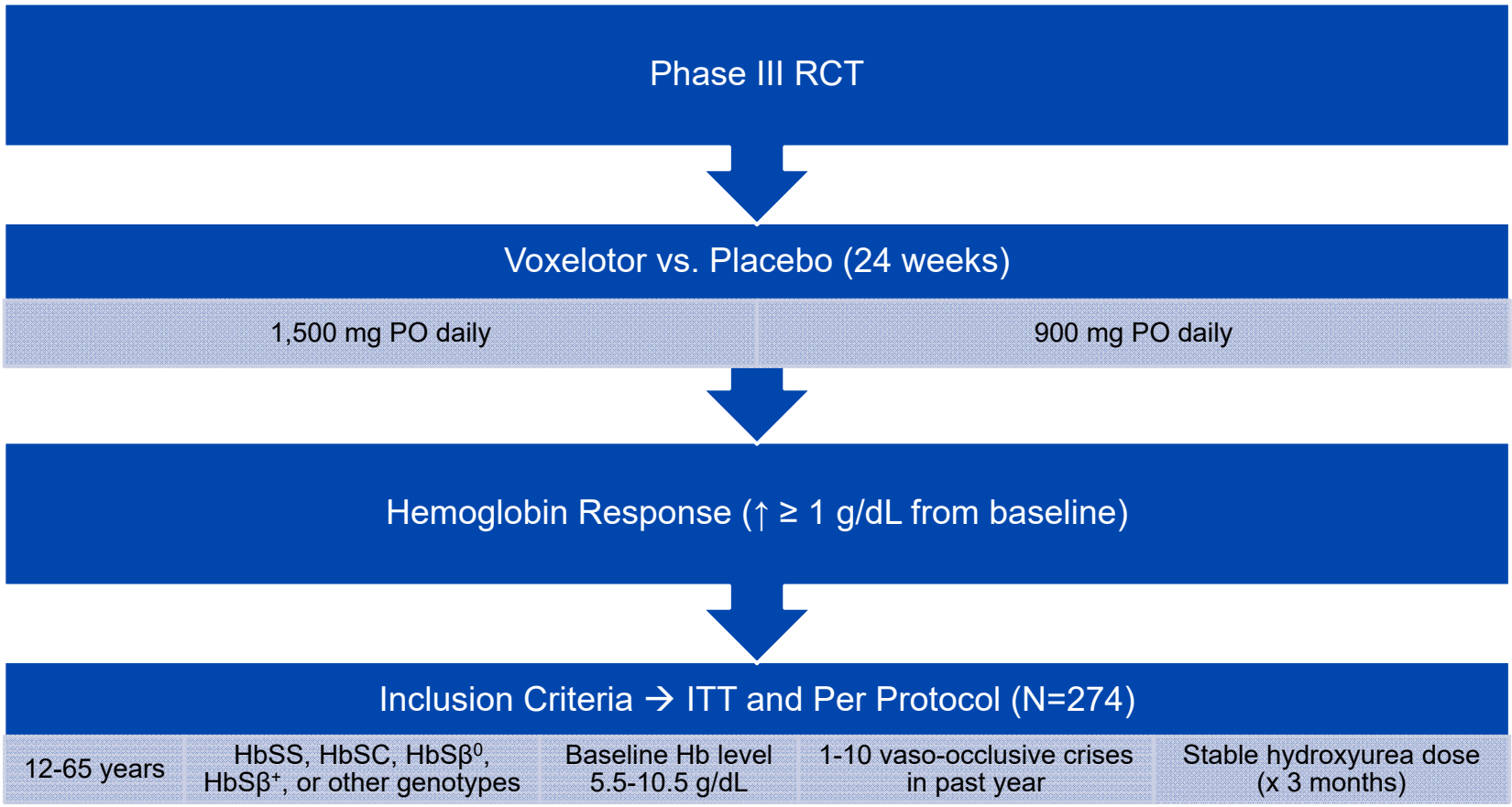
HOPE Trial (2019)



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ITT: Intention to treat

Baseline Characteristics

Characteristic	1,500 mg (N=90)	900 mg (N=92)	Placebo (N=92)
Age (yrs), median (range)	24 (12-59)	24 (12-59)	28 (12-64)
12-17 years, N (%)	14 (16)	15 (16)	17 (18)
HbSS, N (%)	61 (68)	71 (77)	74 (80)
HbSC, N (%)	3 (3)	2 (2)	2 (2)
HbSβ^0, N (%)	18 (20)	13 (14)	11 (12)
HbSβ^+, N (%)	7 (8)	2 (2)	3 (3)
Baseline Hb (g/dL), median (range)	8.7 (5.9-10.9)	8.3 (5.9-10.8)	8.6 (6.1-10.5)
1 crisis in past year, N (%)	35 (39)	41 (45)	39 (42)
2-10 crises in past year, N (%)	55 (61)	51 (55)	53 (58)
Hydroxyurea use, N (%)	58 (64)	63 (68)	58 (63)

Vichinsky et al. (2019). *N Engl J Med*. 381(6):509-519.

Primary Outcome

ITT End Point	1,500 mg (N=90)	900 mg (N=92)	Placebo (N=92)
Hb response at week-24, N (%)	46 (51)	30 (33)	6 (7)
P-value	< 0.001	---	---

Per Protocol End Point	1,500 mg (N=74)	900 mg (N=79)	Placebo (N=76)
Hb response at week-24, N (%)	44 (59)	30 (38)	7 (9)

Vichinsky et al. (2019). *N Engl J Med*. 381(6):509-519.

ITT: Intention to treat

Secondary Outcomes: Laboratory Markers

- 1,500 mg vs. placebo
  - Greater change in Hb level
  - Decreased hemolysis markers

Variable	1,500 mg	900 mg	Placebo
Absolute change in Hb (g/dL)	1.1 (0.9-1.4)*	0.6 (0.3-0.8)	-0.1 (-0.3-0.2)
Indirect bilirubin (%)	-29.1 (-35.9 to -22.2)*	-20.3 (-27.1 to -13.6)	-3.2 (-10.1 to 3.8)
Reticulocytes (%)	-19.9 (-29 to -10.9)*	-1.3 (-10.3 to 7.7)	4.5 (-4.5 to 13.6)
Absolute reticulocyte count (%)	-8 (-18 to 2.1)	5.1 (-4.9 to 15.2)	3.1 (-7 to 13.2)
Lactate dehydrogenase (%)	-4.5 (-11.9 to 2.8)	1.4 (-5.9 to 8.7)	3.4 (-4 to 10.9)

Vichinsky et al. (2019). *N Engl J Med*. 381(6):509-519.

*: P<0.001

Vaso-Occlusive Crisis

Variable	1,500 mg (N=88)	900 mg (N=92)	Placebo (N=91)
Annual vaso-occlusive crisis incidence rate, N (95% CI)	2.77 (2.15-3.57)	2.76 (2.15-3.53)	3.19 (2.5-4.07)
1 or more vaso-occlusive crises, N (%)	59 (67)	61 (66)	63 (69)
Total number of vaso-occlusive crises	179	183	219

Vichinsky et al. (2019). *N Engl J Med*. 381(6):509-519.

Safety Analysis

- Adverse events (≥ 10% incidence)
  - Headache, diarrhea, nausea, extremity pain

	1,500 mg (N=88)	900 mg (N=92)	Placebo (N=91)
Incidence of adverse events of any grade, N (%)	83 (94)	86 (93)	81 (89)

Vichinsky et al. (2019). *N Engl J Med*. 381(6):509-519.

Study Comparison of New Therapies

	L-Glutamine	Crizanlizumab	Voxelotor
Age	5+ years	16+ years	12+ years
Baseline pain crises	≥ 2	≥ 2	≥ 1
Annual pain crisis incidence	↓ 25%	↓ 45%	No significant effect
Median time to pain crisis	↓	↓	N/A
Effect on Hb	N/A	N/A	↑
Adverse effects	Constipation Nausea Headache	Headache Back pain Nausea	Headache Diarrhea Nausea

Niihara et al. (2018). *N Engl J Med*. 379(3):226-235.
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Prescribing Considerations

	L-Glutamine	Crizanlizumab	Voxelotor
Cost	$	$$	$$$
Formulation	Oral Packet	Intravenous	Oral Tablet
Administration Frequency	Twice daily	Week 0 and 2 then Every 4 weeks	Daily
Procurement	Specialty Rx	Infusion therapy center	Specialty Rx
Prior authorization(?)			
+/- Co-pay assistance			

Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.

Learning Objective Question #3

- CP is a 16 yo F with HbSS who is compliant with her current hydroxyurea therapy. Her pain has become unmanageable and she has visited the ED 4 times in the past 2 months. What would be a reasonable therapy to trial at this time?
  A. Blood transfusions
  B. L-glutamine
  C. Crizanlizumab
  D. Voxelotor

Summary

- Describe the pathophysiology and complications associated with sickle cell disease
  - Genetic disorder characterized by distortion and adhesion of RBCs leading to multisystem acute and chronic sequelae
- Review standard treatment modalities of sickle cell disease
  - Mainstay of management is stem cell transplant, RBC transfusions, infection prophylaxis, and hydroxyurea
- Discuss recent literature regarding advancements in sickle cell disease therapy
  - L-glutamine, crizanlizumab, and voxelotor may have an additive role in improving sickle cell disease management

MAYO CLINIC

Questions & Discussion

Hydroxyurea: BABY HUG (2011)

- Phase III RCT
  - Determine if hydroxyurea can prevent onset of chronic end organ damage in young children with SCD
- Hydroxyurea (20 mg/kg/day) vs. placebo
  - Did not allow dose escalation in treatment arm
    - Not fully optimizing therapy
- Results
  - Hydroxyurea associated with lower rates of pain, dactylitis, acute chest syndrome, required transfusions, and gastroenteritis
  - No clinically relevant adverse effects
  - No significant difference between groups in primary endpoint

Wang et al. (2011). *Lancet*. 377(9779):1663:1672

Hydroxyurea Monitoring

- Prior to initiation:
  - CBC with reticulocyte count
  - Liver function tests
  - Pregnancy test
- CBC every 4 weeks
- Annually:
  - HbF level
    - Goal > 30%
- Stop therapy when:
  - ANC < 1500-3000/mcL
  - Plt < 80k/mcL

Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.

Infection Prevention: Immunizations

Pneumococcal

- PCV13
  - 4 doses
    - 2, 4, 6, 12-15 months
  - Minimum 4 weeks between first 3 doses
  - Minimum 2 months between 3rd and 4th dose
- PPSV23
  - 2 doses (24 months, 3-5 years after 1st dose)

Meningococcal

- Quadrivalent meningococcal
  - 2-4 doses
  - Approved from as young as 8 weeks old
  - Booster every 5 years
- Serogroup B meningococcal
  - 2-3 doses
  - ≥ 10 years old

Centers for Disease Control and Prevention (2020).
National Heart Lung and Blood Institute (2014).
Telen et al. (2019). *Nat Rev Drug Discov*. 18(2):139-158.

