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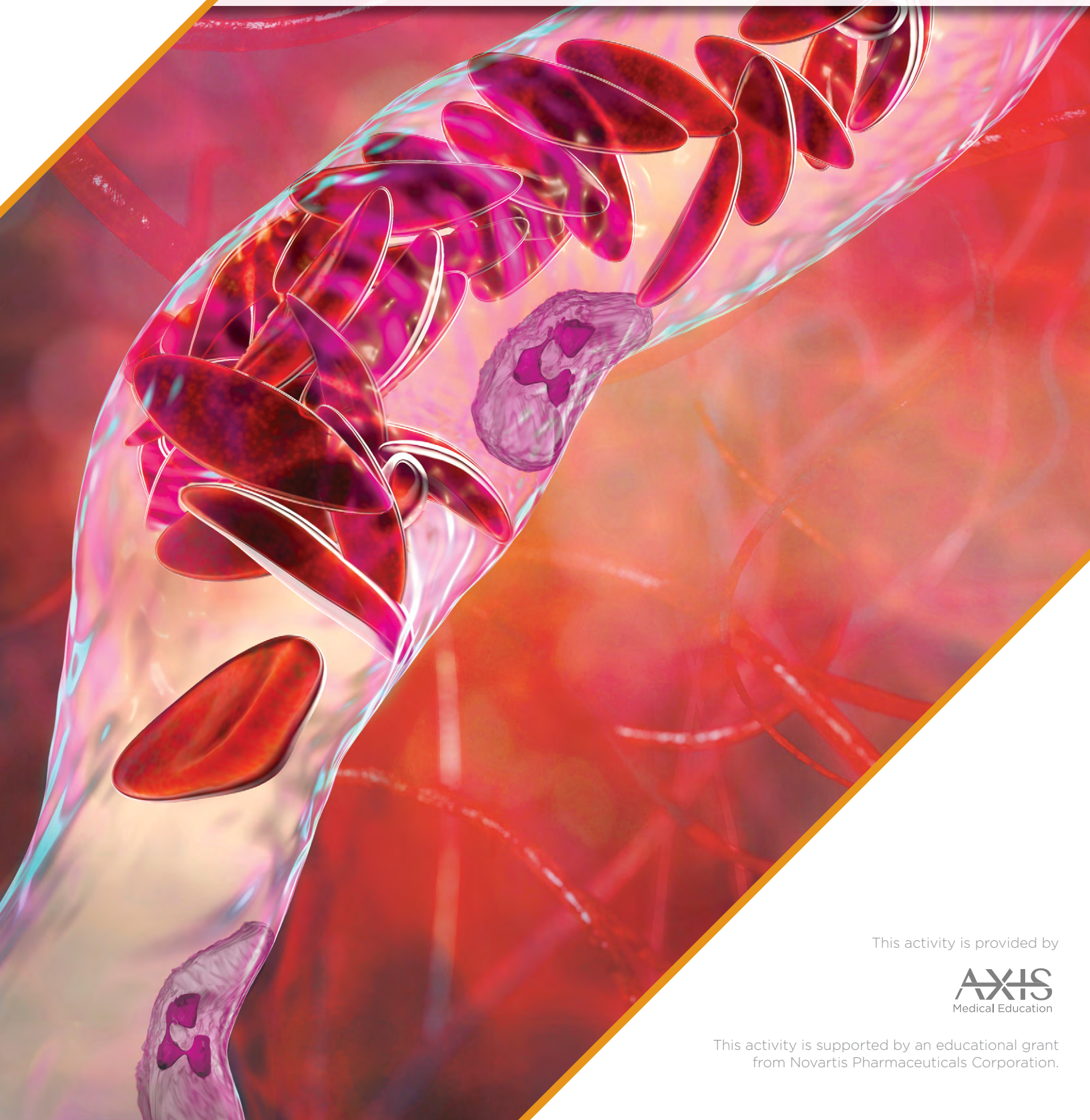
Novel Interventions for Preventing/ Reducing Pain Crisis in Sickle Cell Disease

This transcript has been edited for style and clarity and includes all slides from the presentation.



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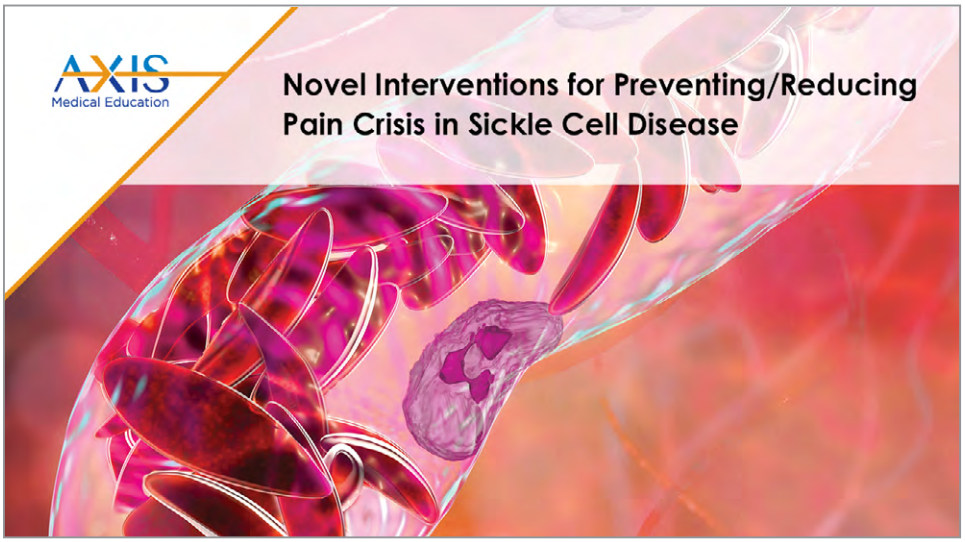
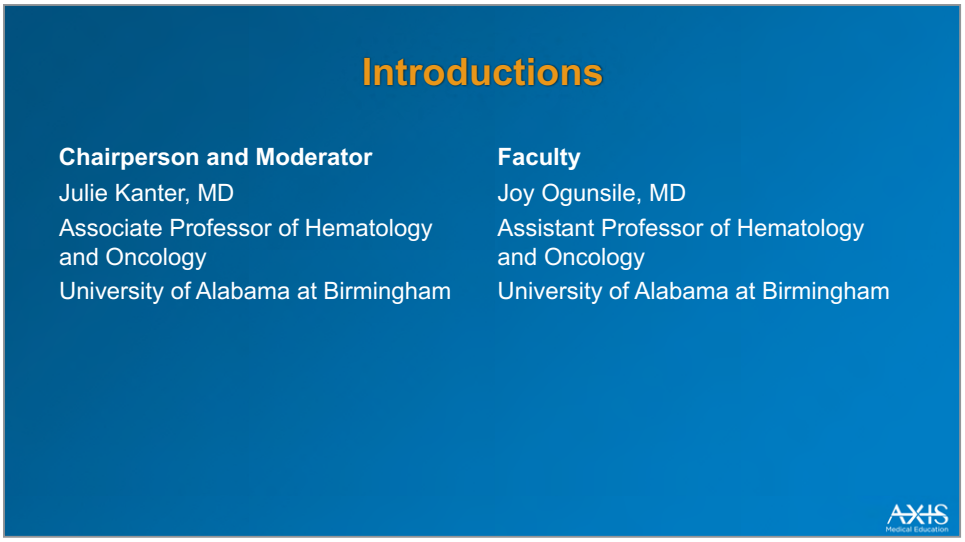
Novel Interventions for Preventing/Reducing Pain Crisis in Sickle Cell Disease

Julie Kanter, MD | Foluso "Joy" Ogunsile, MD

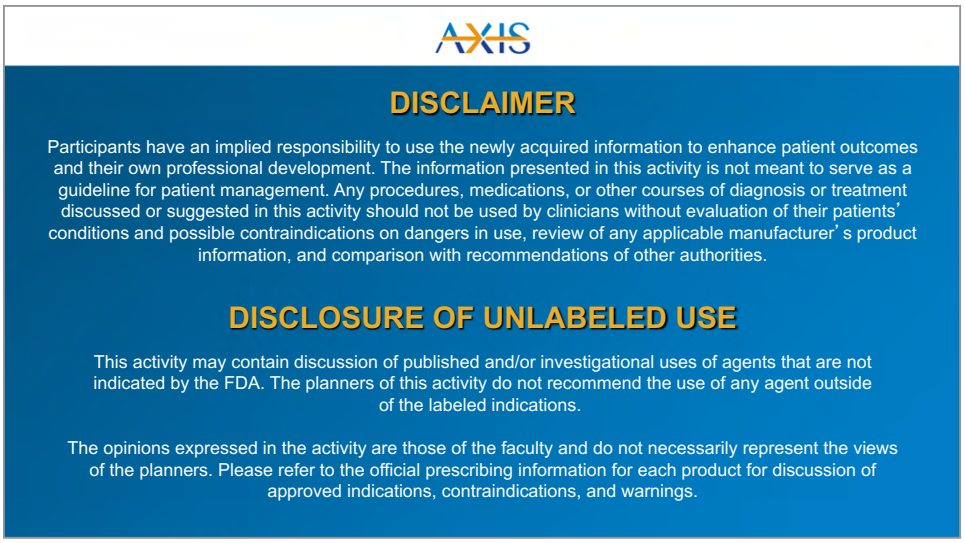


Julie Kanter, MD: Hello and welcome to this educational activity entitled, "*Novel Interventions for Preventing and Reducing Pain Crisis in Sickle Cell Disease*."



I am Dr. Julie Kanter, Associate Professor of Hematology and Oncology at the University of Alabama at Birmingham. I am lucky to be joined today by Dr. Joy Ogunsile, Assistant Professor of Hematology and Oncology at the University of Alabama at Birmingham.

Foluso "Joy" Ogunsile, MD: Thank you, Dr. Kanter, it's a pleasure to be here with you today.



- **Kanter:** Please note that there is a disclaimer and disclosure that we may refer to some off-label agents or agents in development.

- We also have financial disclosures for your review.

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Examine acute and chronic complications associated with sickle cell disease (SCD)
- Formulate optimal treatment plans for the management of SCD based on the efficacy and safety of disease-specific therapies and current guideline recommendations
- Formulate optimal treatment plans for acute pain management in patients with SCD presenting with a vaso-occlusive crisis (VOC)
- Evaluate data on novel therapies for the prevention of VOC in patients with SCD and how they may be utilized in future management strategies

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In brief, here are the learning objectives for this activity today. We want to examine acute and chronic complications associated with sickle cell disease. We want to formulate optimal treatment plans for the management of individuals with sickle cell disease based on efficacy and safety of disease-specific therapies and current guideline recommendations. We also want to formulate optimal treatment plans for acute pain management in individuals presenting with acute crisis or vaso-occlusive crises (VOCs). Finally, we'll evaluate data on novel therapies for the prevention of VOC in patients with sickle cell disease and how they may be used in future management strategies.

US Sickle Cell Disease Population

- Calculation based on birth prevalence and census data, correcting for early mortality:
  - Total: ~100,000 individuals
    - 60% adults (at least)
    - 90% Black, 10% Hispanic
  - Genotype distribution in the United States
    - At birth: HbSS 60%; HbSC 30%; HbSβ-thalassemia 10%
    - In adulthood:
      - At age 30: HbSS 50%
      - At age 60: HbSS 25%

HbSS, sickle cell anemia; HbSC, sickle cell with hemoglobin C disease; HbSβ, hemoglobin S-beta.
Hassell et al. *Am J Prev Med.* 2010;38:S512; Brousseau et al. *Am J Hematol.* 2010;85:77.

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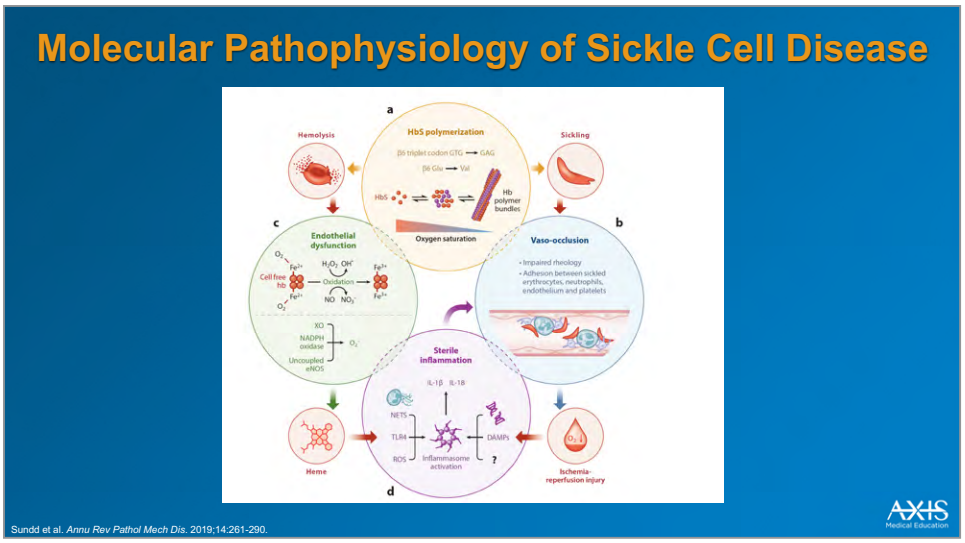
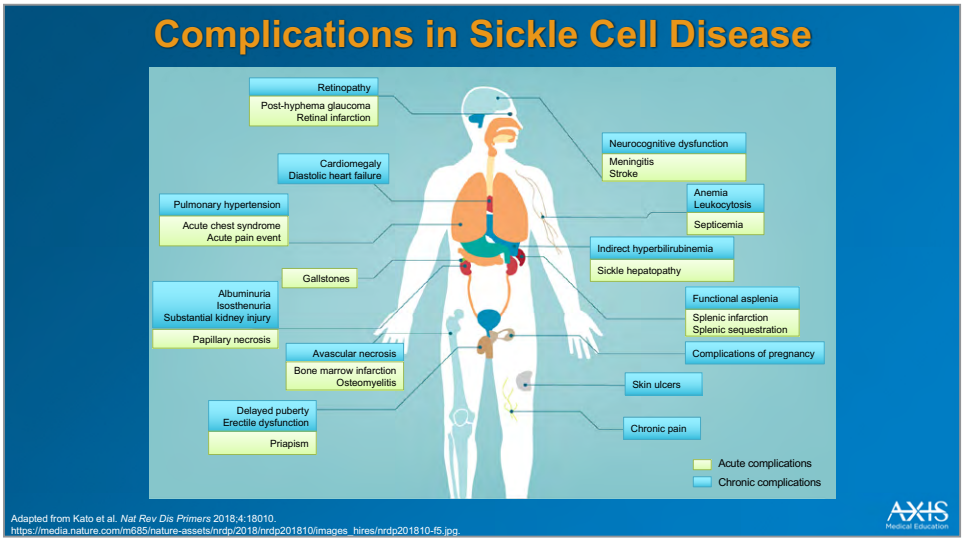
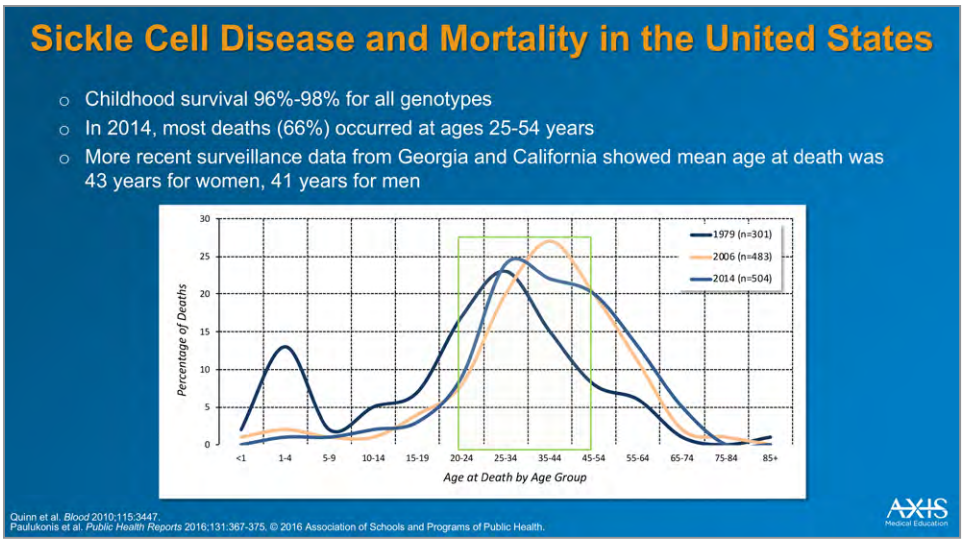
Let's start with a review of sickle cell disease and associated complications. Even though sickle cell disease is a rare disease, it is fairly common in the United States and affects up to 100,000 individuals. At least 60% of those individuals are adults. In the United States, approximately 90% of affected individuals are black and around 10% are Hispanic. When we look at genotypes present in the United States, roughly 60% have hemoglobin SS type disease, around 30% have SC disease, and the other 10% is mostly represented by Sβ-thalassemias.



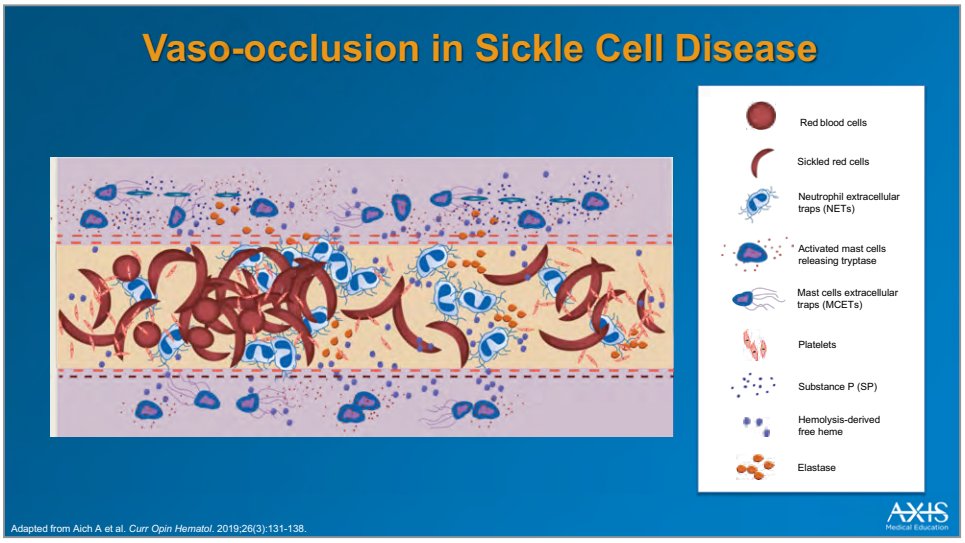
- Let's start with the molecular pathophysiology of sickle cell disease. Starting in the first circle on the top, we know the primary initial problem in sickle cell disease is the abnormal sickle hemoglobin. That hemoglobin polymerizes when deoxygenated, resulting in the characteristic sickle shape of a red blood cell. We also know those red blood cells are fragile and easily break apart, releasing free heme. That free heme causes ongoing endothelial dysfunction and inflammation. This inflammation is then perpetuated by white blood cells and platelets. Together, platelets, white cells, and sickled hemoglobin will result in vaso-occlusion. Although it seems like these events are discrete, we know they overlap during both steady state and during a vaso-occlusive crisis.



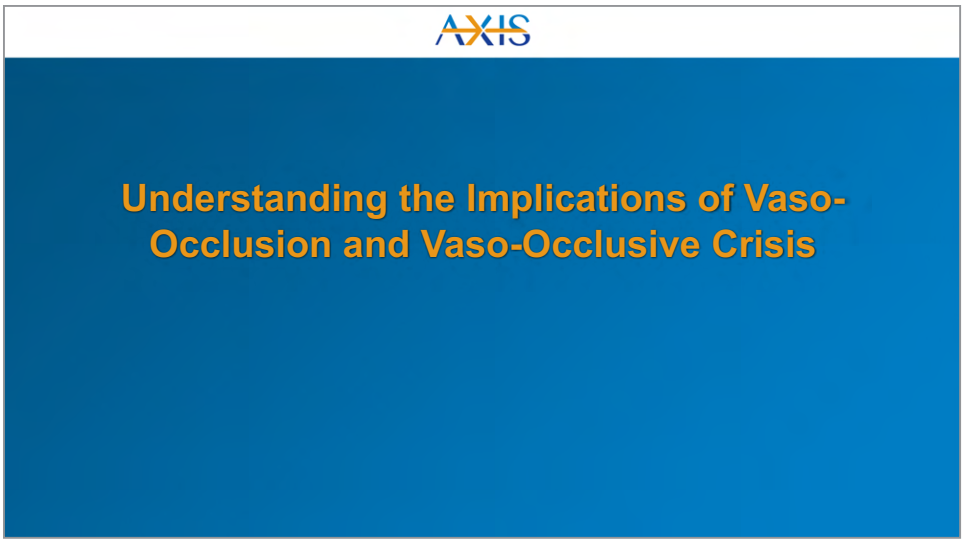
- The result of this is significant complications that affect every organ in the body. Unfortunately in sickle cell disease, there's not a single organ that is unaffected. Brain, kidneys, lungs, skin, muscle, bone, and even teeth are affected in sickle cell disease. We don't have time to review all of the complications, but please note that every organ system can be affected by this disease.



- We've seen significant improvement in sickle cell disease and mortality in children in high resource countries. Childhood survival is 96% to 99% for all genotypes. Although this is really exciting, we are not seeing the significant improvement in adults. Unfortunately, we still have many deaths in 25- to 54-year-old patient group. The surveillance data from Georgia and California has given us our most recent information still showing that the average lifespan, unfortunately, is only 41 to 43 years. When you look at this graph, I want to point out the most recent 2014 data, which continues to show the significant increase in mortality in young adults. We clearly need new agents to improve outcomes in sickle cell disease.



- As a quick reminder about VOCs in sickle cell disease, it is truly a multicellular adhesive process. It is not just sickled red blood cells; but instead, it's sickled red blood cells, neutrophils, platelets, and the endothelium interacting. Dr. Ogunsile, can you tell us a little more about VOCs in sickle cell disease?



Ogunsile: Sure, Dr. Kanter. So let's transition to understanding the implications of vaso-occlusion and VOCs.

To begin, we'll start with a discussion of pain. Pain is well known to be the hallmark of sickle cell disease. It is the primary reason people seek care. We think that this pain is due primarily to vaso-occlusion. Pain is present throughout life in more than 50% of affected individuals. However, it's always important to remember that not all pain in sickle cell disease is VOC pain. And that patients with sickle cell disease can have pain due to other reasons.

VOCs – What Are They, and Why Do They Occur?

- Normal red blood cells (RBCs) are doughnut shaped and flexible, rolling through the vasculature supplying oxygen and nutrients to the body[1]
- RBCs with sickle cell hemoglobin have different properties and are more likely to stick to the cells (endothelium) on the inside of the blood vessel
- White blood cells and activated endothelial cells can also trigger adhesive interactions with sickled RBCs, other white blood cells, and platelets due to chronic vascular damage[3]
- Blockage of small blood vessels results in vaso-occlusion
- *VOCs: Recurrent episodes of vaso-occlusion can lead to severe unpredictable acute pain that may require hospitalization[2-5]

VOCs, vaso-occlusive crises.
1. CDC. https://www.cdc.gov/dotw/sickle-cell-disease/. 2. Rees et al. *Lancet*. 2010;376(9757):2018-2031.
3. Piel et al. *N Engl J Med*. 2017;376:1561-1573. 4. Zhang et al. *Blood*. 2016;127(7):801-809. 5. Habara and Steinberg. *Exp Biol Med*. 2016;241(7):689-696.

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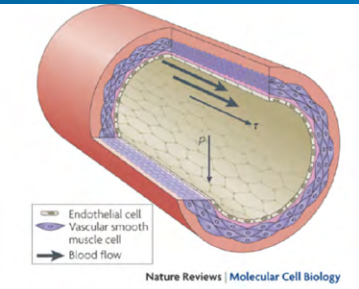
- VOCs—what are they and why do they occur? So normally, red blood cells are doughnut shaped and flexible, rolling through the vasculature supplying oxygen and nutrients to the body. However, in sickle cell disease, the red blood cells are sickled and have different properties, so that they're more likely to stick to the endothelial cells and the inside of the blood vessels. In addition, white blood cells and activated endothelial cells can trigger adhesive interactions with sickled red blood cells and other white blood cells and platelets due to chronic vascular damage. So they are also playing a role.

  This all contributes to the blockage of small blood vessels, which results in vaso-occlusion. So when we think of VOCs, these are recurrent episodes of vaso-occlusion that can lead to severe unpredictable acute pain that may require hospitalizations in people with sickle cell disease.

The Role of the Endothelium

- Endothelial cells also play a pivotal role in regulating blood flow and fluid filtration
- Participate in hemostasis and neutrophil recruitment
- Alterations of *endothelium* affect multiple areas of the body and contribute to:
  - Peripheral vascular disease
  - Stroke
  - Heart disease
  - Chronic kidney failure in several disease states
  - Venous thrombosis
  - And several other pathologic processes



Hahn C, Schwartz MA. *Natl Rev Mol Cell Biol*. 2009;10:53-62.

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- The role of the endothelium is important in vaso-occlusion. Endothelial cells also play a pivotal role in regulating blood flow and fluid filtration. They are very important in participating in hemostasis and neutrophil recruitment. Alterations of endothelium affect multiple areas of the body and contribute to peripheral vascular disease, stroke, heart disease, and chronic kidney disease, among other conditions.

Long-term Impact of Vaso-occlusion on Organs

- Ongoing vaso-occlusion and VOCs are associated with increased risk for organ damage, organ failure, and death[1-4]
- Damage occurs due to vaso-occlusion (lack of oxygen), blood vessel damage, and secondary complications
- Ongoing inflammatory response, cell activation, and multicellular adhesion contribute to tissue damage
- **Vaso-occlusion and VOCs are associated with **decreased organ function and can result in life-threatening complications** such as acute chest syndrome, pulmonary hypertension, renal failure, and stroke[7,8]

VOCs, vaso-occlusive crises.
1. Belcher et al. *Am J Physiol Heart Circ Physiol*. 2005;288:H2715-H2725. 2. Powars et al. *Medicine (Baltimore)*.2005;84(6):363-376.
3. Elmariah et al. *Am J Hematol*. 2014;89(5):530-535. 4. Platt et al. *N Engl J Med*. 1994;330(23):1639-1644.
5. Nath Grande et al. *Am J Pathol*. 2005;166(4):963-972. 6. Tran et al. *Blood* 2017;130(22):2377-2385.
7. Ballas et al. *Blood* 2012;120(18):3647-3656. 8. Piel et al. *N Engl J Med*. 2017;376(16):1561-1573.

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- Ongoing vaso-occlusion and VOCs are associated with increased risk for organ damage, organ failure, and death. Damage occurs due to vaso-occlusion, blood vessel damage, and secondary complications, as discussed before. It's important to remember that ongoing inflammatory responses, cell activations, and multicellular adhesions contribute to tissue damage. Vaso-occlusions and VOCs are associated with decreased organ function and can result in life-threatening complications.

SCD Can Affect Quality of Life for Children and Adults

- Emotional complications of SCD include depression, anxiety, catastrophizing
- Affected individuals often have to miss school/work due to SCD-related complications
- Concerns for VOC may prevent individuals from engaging with others or pursuing certain activities

SCD, sickle cell disease; VOC, vaso-occlusive crisis.
Rizio et al. *Value Health* 2017;20:A679-A680. Kato et al. *Nat Rev Dis Primers*. 2018;4:18010.

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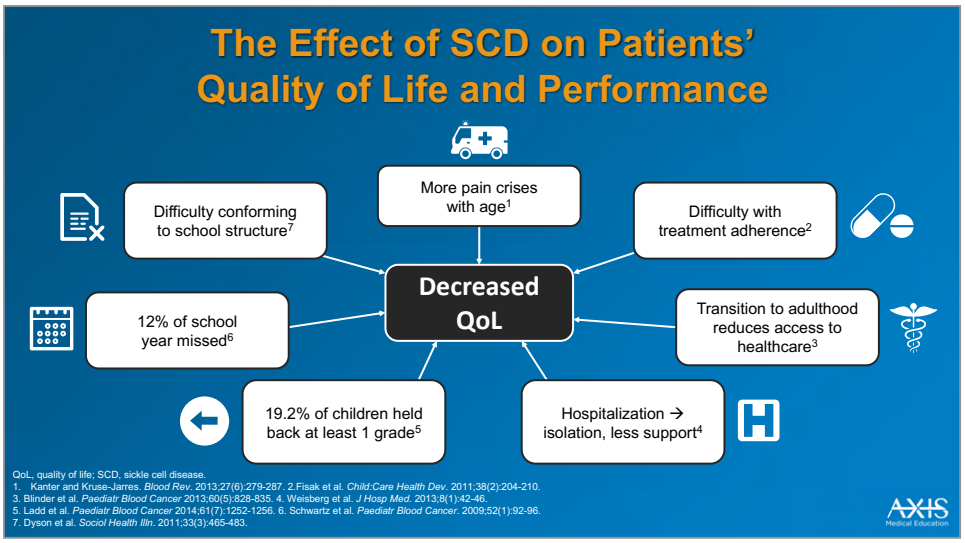
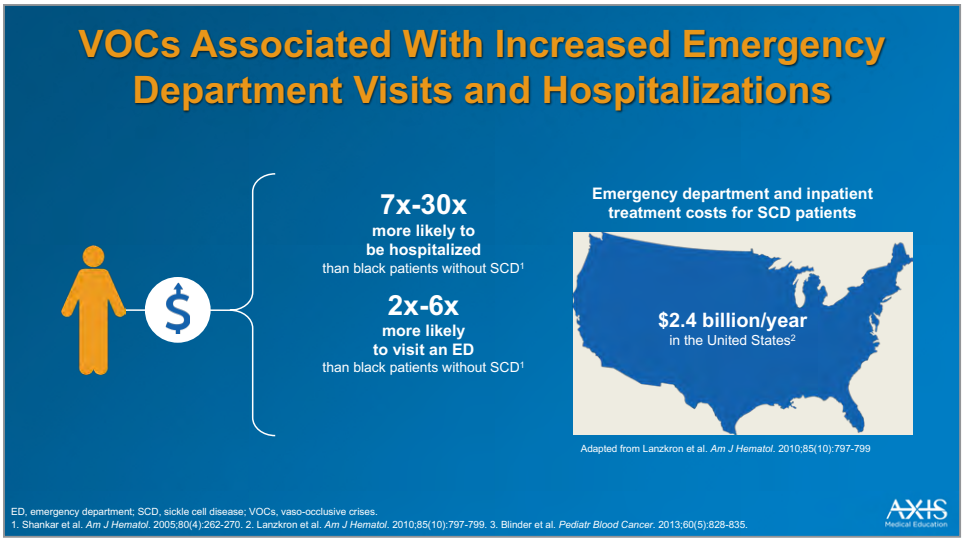
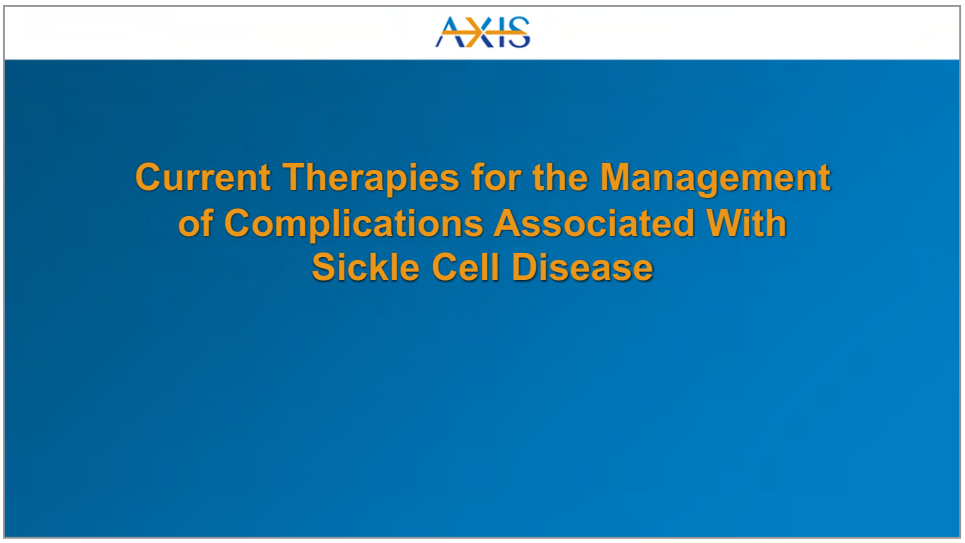
- Vaso-occlusion can also affect the quality of life of children and adults. Psychological complications in sickle cell disease include depression, anxiety, and catastrophizing. Affected individuals often have to miss school/work due to sickle cell disease–related complications. In addition, their concerns about VOC may prevent individuals from engaging with others or pursuing certain activities.



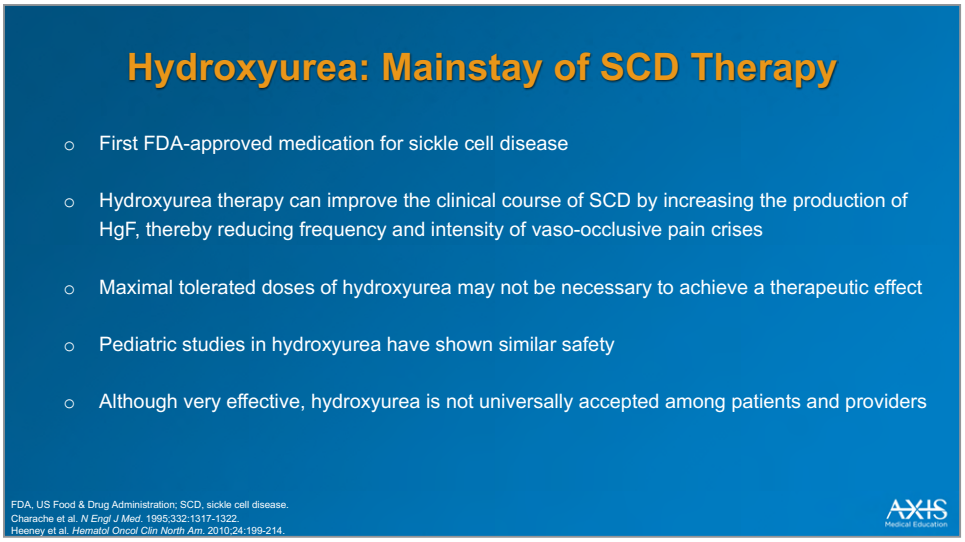
- Multiple studies have shown that the effects of sickle cell disease can affect quality of life for people living with this disease. Results from multiple studies show that pain increases with age, and thus can decrease quality of life. People living with sickle cell disease have difficulty with treatment adherence due to vaso-occlusion that occurs in the brain and cognitive impairment. There is difficulty with transitioning to adulthood due to reduced access to healthcare and hospitalizations that isolate them from social support. There are also issues academically. All these things contribute to decreased quality of life in these patients.



- VOCs are associated with increased emergency department visits and hospitalizations with increased morbidity compared to blacks in the United States. Black patients with sickle cell disease are 7 to 30 times more likely to be hospitalized than black patients without sickle cell disease. Moreover, they're 2 to 6 more times more likely to visit an emergency department than blacks without the disease, resulting in an increased cost utilization of $2.4 billion a year.



Kanter: Thank you. I think quality of life is so important when we talk about sickle cell disease and is especially important when we discuss the current available therapies, including hydroxyurea, L-glutamine, blood transfusion, stem cell transplant, and pain management. We're going to review these current therapies now.



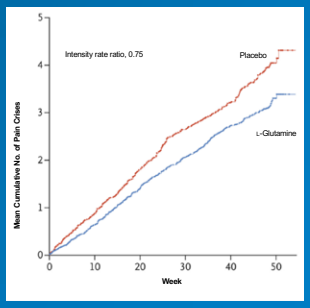
Hydroxyurea remains the mainstay of therapy for sickle cell disease. It was the first FDA-approved medication that was shown to decrease the occurrence of acute VOCs. We also know that maximum tolerated doses of hydroxyurea are not always necessary for therapeutic effect. Pediatric studies have also shown that it is safe and highly effective in children with sickle cell disease.

New Kid on the Block: L-Glutamine

Phase 3 trial of L-glutamine in SCD

- 25% reduction in number of pain crises
  - Median: 3.0 vs 4.0; *P* < .005
- 30% lower hospitalization rates
  - Median: 2.0 vs 3.0; *P* < .005
- Reduced number of episodes of acute chest syndrome
  - ≈8% vs 23%; *P* < .005

Number Of Sickle Cell–related Pain Crises Over Time



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

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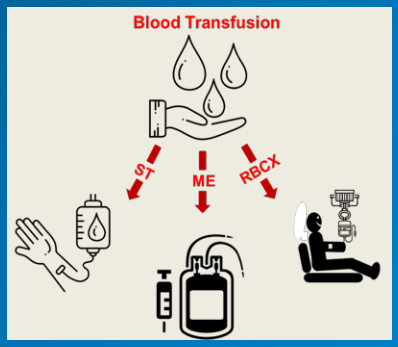
- L-glutamine is really the new kid on the block. Now this is pharmaceutical grade L-glutamine; not the same L-glutamine that you're going to buy at GNC or another health food store. In a phase 3 trial of L-glutamine, there was a 25% decrease in the number of pain crises. We also saw 30% lower hospitalizations and a reduced number of patients with acute chest syndrome.

Transfusion Therapies: Three Therapeutic Modalities

- Blood transfusion is a disease-modifying therapy for the treatment and prevention of acute and chronic complications of SCD[1]
- Blood may be administered by:
  - Simple transfusion[1]
  - Manual exchange
  - Automated red blood cell exchange
- Main complications of transfusion[1,2]:
  - Alloimmunization
  - Iron overload
  - Hyper-hemolytic transfusion reactions
  - Transfusion-associated circulatory overload



ME, manual exchange; RBCX, red blood cell exchange; SCD, sickle cell disease; ST, simple transfusion
1. Howard. *ISBT Science Series* 2013;8:225-228; 2. Agnihotri and Agnihotri. *Indian J Crit Care Med*. 2014;18(6):396-398.

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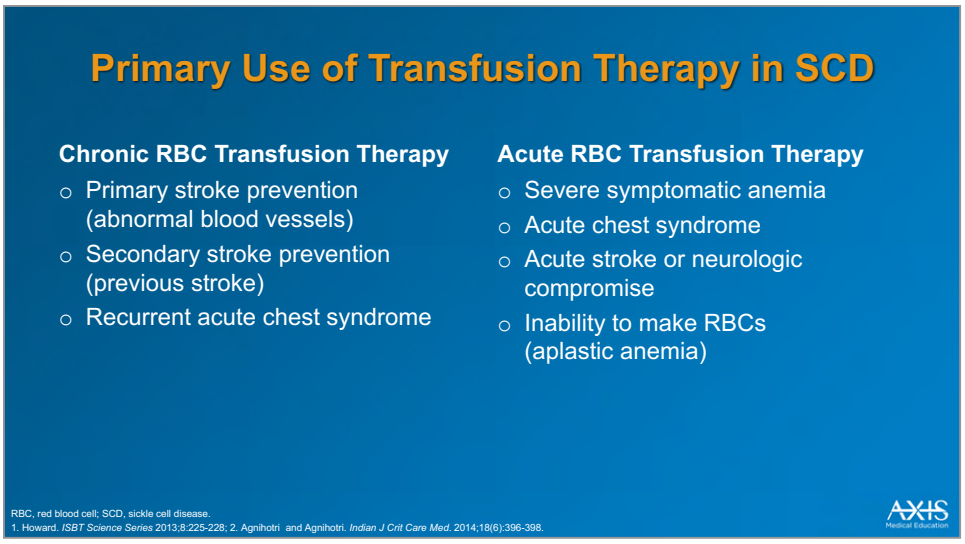
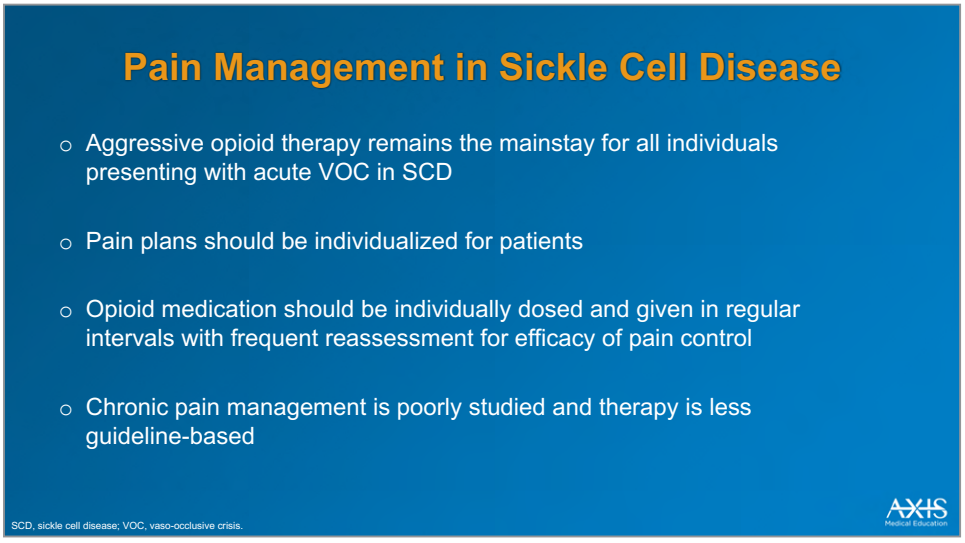
- When we think about transfusion therapy, there are 3 main ways we give transfusions. We give them by simple transfusions, manual exchanges, or automated red blood cell exchanges using apheresis. There are, unfortunately, several complications associated with transfusion therapy. Alloimmunization occurs when an individual may build antibodies to red cells, iron overload, hyperhemolytic transfusion reactions, as well as transfusion-associated circulatory overload.

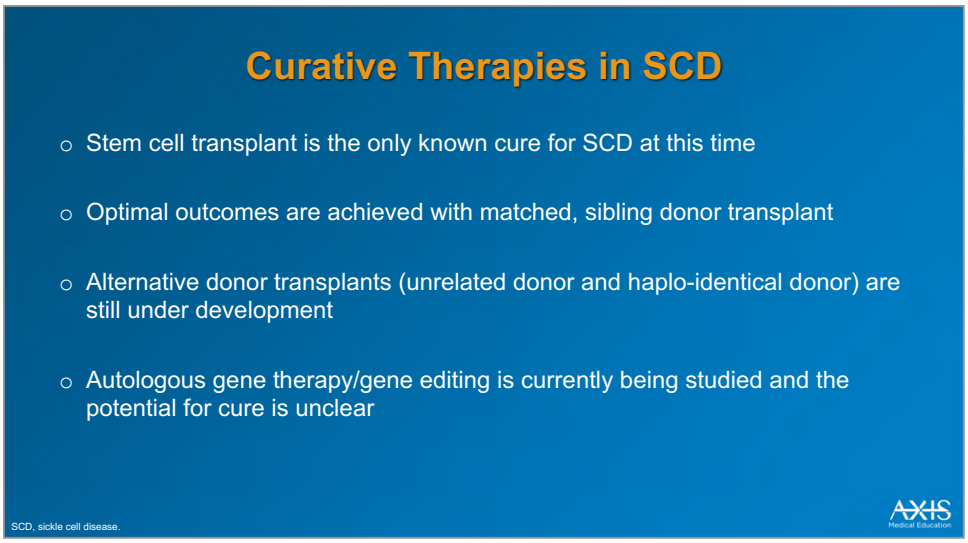


So why do we use transfusions in sickle cell disease? Well primarily, we use chronic transfusion therapy for stroke prevention. This can be for primary stroke prevention in the individuals who have abnormal blood flow in the brain who have not experienced a stroke; or for secondary stroke prevention in individuals who have, unfortunately, had a stroke. We've also seen efficacy in individuals who have had recurrent acute chest syndrome.

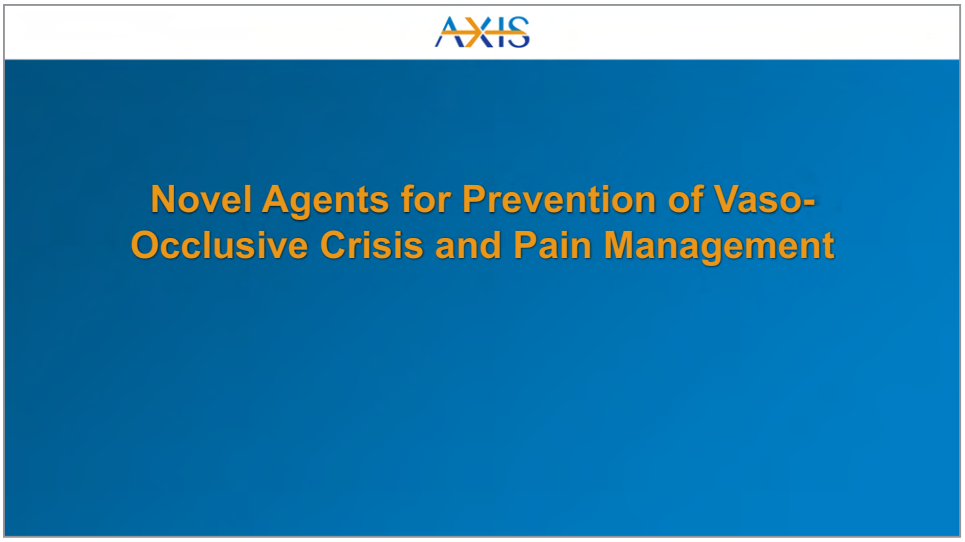
In the acute setting, we sometimes need transfusions as well. This can be for severe symptomatic anemia, for acute chest syndrome, for someone who has an acute stroke, or someone who cannot make red blood cells usually caused by a virus. It is important that we do not use transfusions for simple VOCs and reserve them for when they are most needed.



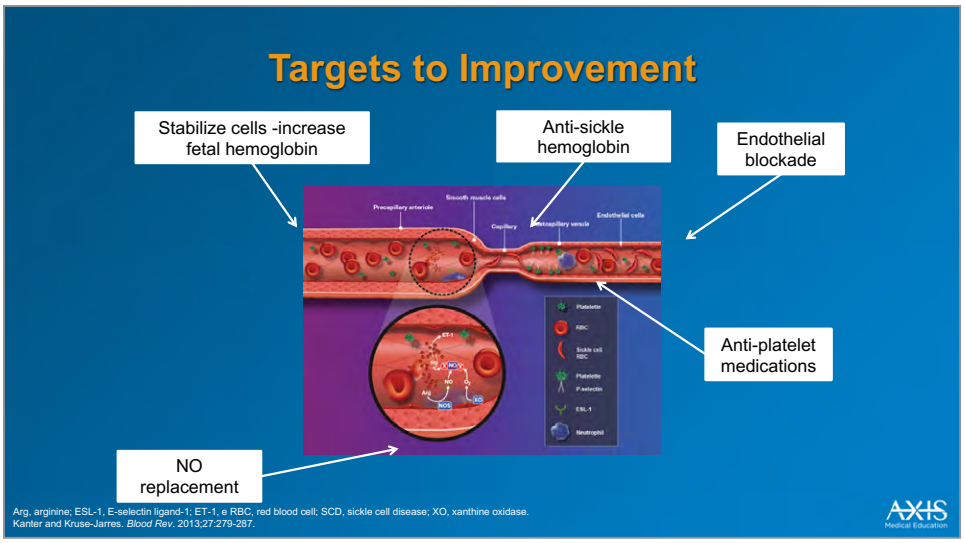
What about pain management in sickle cell disease? Without question, aggressive opioid therapy is the mainstay for acute VOCs in sickle cell disease, and that is intravenous opioid therapy. Pain plans must be individualized for affected patients. Opioid medication should be dosed individually given in regular intervals with frequent reassessment to assess the effect of that pain control. Chronic pain management remains poorly understood. Therapy is less guideline based and should be assessed on an individual basis.



- There are curative strategies in sickle cell disease. Stem cell transplant is a known cure for sickle cell disease. We know that optimal outcomes are achieved when individuals have a matched sibling donor. However, unfortunately, many individuals do not have a matched donor. As a result, we are studying alternative donors with either unrelated donors or half-matched donors, and these are in development. We are also trying to identify if autologous gene therapy and gene editing are options for cure for sickle cell disease.



- Now let's look at the novel therapies for prevention of sickle cell disease.



I want to start first with looking at the targets that we're looking to improve. When we look at the blood vessel and the different components that we talked about in sickle cell VOCs, we note that one of the first things we can target is the red blood cell itself. We can attempt to stabilize the hemoglobin inside the red blood cell or increase the fetal hemoglobin, or baby hemoglobin, which prevents sickling.

The next major target we want to talk about is whether we can prevent that hemoglobin from sickling with a small molecule that binds to the hemoglobin itself. We want to prevent adhesion to the endothelium. This can both prevent vaso-occlusion but also, hopefully, prevent some of the scarring that can occur. We are also looking at anti-platelet medications to see how this can help reduce VOCs.

And finally, hemolysis—or the release of free heme—remains toxic and inflammatory to the bloodstream. We are also trying to understand if nitric oxide replacement can help combat this inflammation.

Dr. Ogunsile, can you tell us about the new therapies in development for sickle cell disease?

Ogunsile: Sure, Dr. Kanter.

GBT440 (Voxelotor)

- Oral, once-daily, direct-acting hemoglobin modifier
- Prevents sickling of RBCs: increases hemoglobin's affinity for oxygen, inhibits polymerization of HbS, restores normal RBC function in preclinical SCD models
- Phase 2/3 trial of GBT440 in SCD started in December 2016

HbS, hemoglobin S; RBCs, red blood cells; SCD, sickle cell disease.
Dufu et al. *Blood* 2014;124:217.
NCT02285088.

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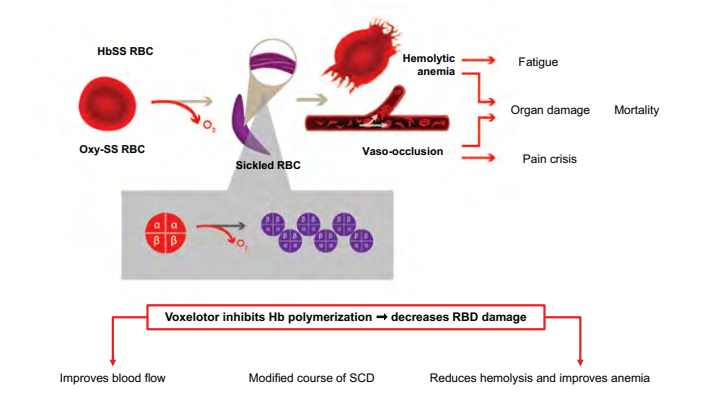
- I will start by talking about GBT440 (voxelotor). It's a once-a-day agent that, in preclinical trials, showed that it prevented sickling of red blood cells.

Voxelotor Trials



Deoxy, deoxygenated; Hb, hemoglobin, HbS, sickle hemoglobin; O_2, oxygen; oxy, oxygenated; RBC, red blood cell; SCD, sickle cell disease; SS, sickle cell anemia.
Adapted from Lehrer-Graiwer et al, 2016.
https://clinicaltrials.gov/ct2/show/NCT03036813. https://clinicaltrials.gov/ct2/show/NCT02850406.

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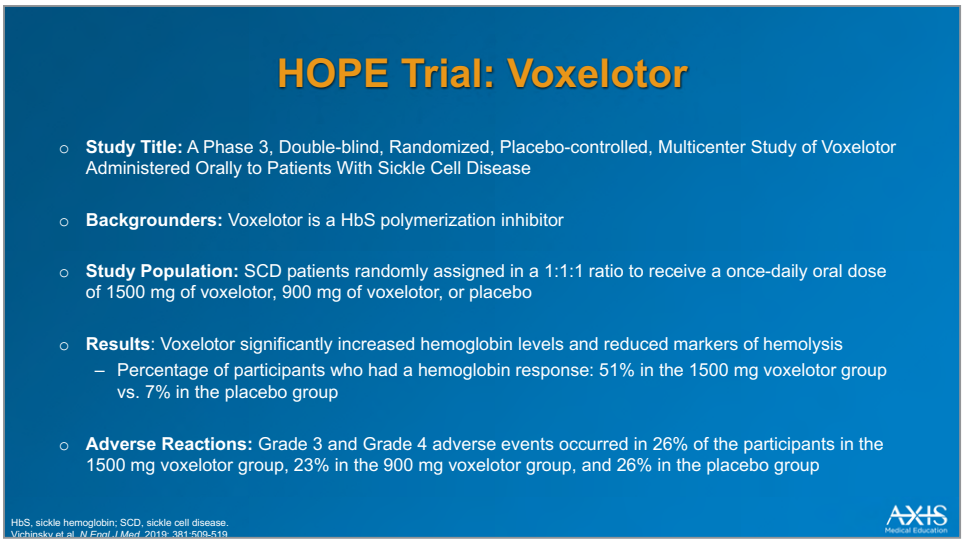
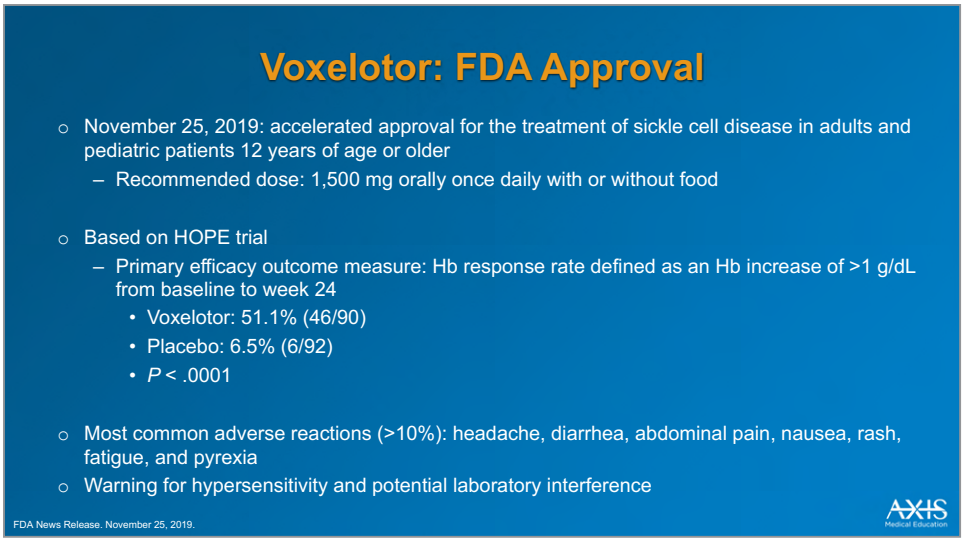
- The voxelotor trials were designed to see its anti-polymerization decreases fatigue, organ damage, mortality, and pain crisis. Voxelotor inhibits hemoglobin polymerization, decreasing red blood cell damage and reducing hemolysis and improves anemia.

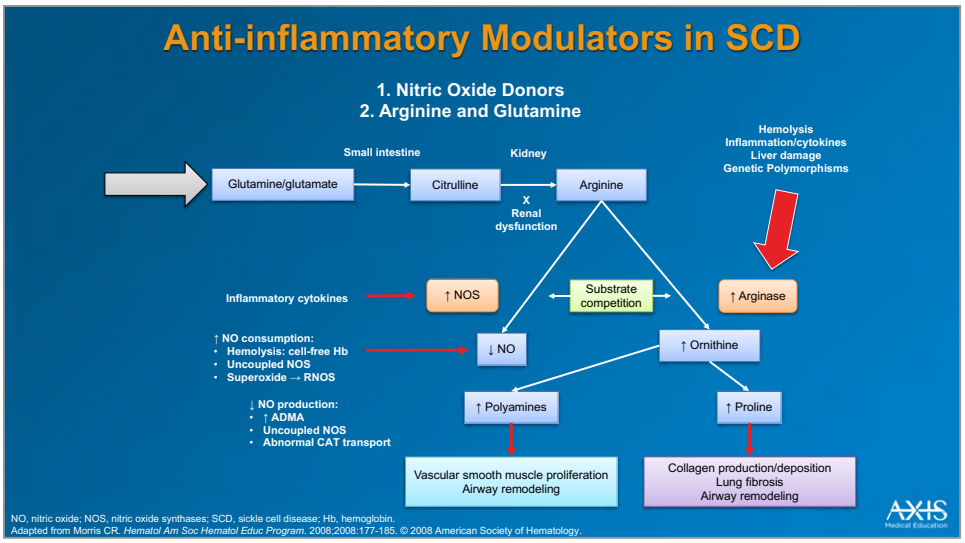


- The results of the trial showed that voxelotor significantly increased hemoglobin levels and reduced markers of hemolysis.

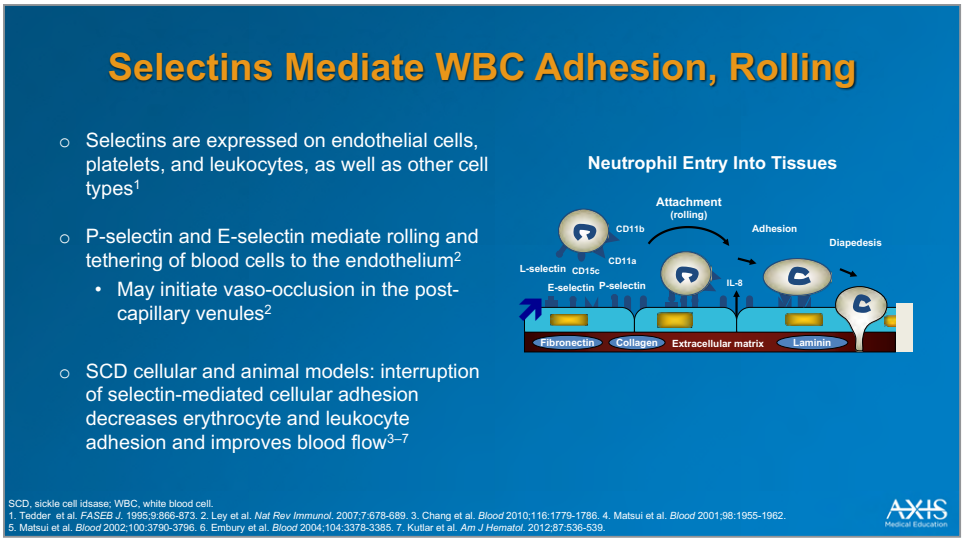
  Kanter: It is very interesting. The voxelotor trials clearly improve hemoglobin, but we'll have to wait long term to see if there's any effect on organ damage or pain crises.



- In November 2019, the FDA granted accelerated approval to voxelotor for the treatment of sickle cell disease in adults and pediatric patients 12 years of age and older based on results of the HOPE trial.



- Reducing inflammation is also important in sickle cell disease as well as reducing cellular adhesion. Anti-inflammatory modulators in sickle cell disease include nitric oxide donors, arginine, and glutamine.



- Selectins mediate the white blood cell adhesion and rolling in sickle cell disease. Selectins are expressed on endothelial cells, platelets, and leukocytes, as well as other cell types. Selectins act like hooks to hold onto the white blood cells, platelets, and red blood cells as they roll through the endothelium. In fact, selectins themselves can actually initiate vaso-occlusion when the neutrophil binds to the inside of the endothelium. In sickle cell disease cellular and animal models, interruption of the selectin-mediated cellular adhesion can decrease erythrocyte and leukocyte adhesion and actually prevent vaso-occlusion.

SUSTAIN Trial: Crizanlizumab

- **Study Title:** A Phase II, Multicenter, Randomized, Placebo-Controlled, Double Blind, 12-Month **Stu**dy to Assess **S**afety and Efficacy of SelG1 With or Without Hydroxyurea **T**herapy in Sickle Cell Disease Patients with Sickle Cell-Related **Pain** Crises
- **Background:** Crizanlizumab is a humanized monoclonal antibody to P-selectin
- **Study Population:** SCD patients (16-65 years of age) who have experienced between 2 and 10 sickle cell-related pain crises within the preceding 12 months
- **Results**: Median annual rate of sickle cell pain crisis was **REDUCED by 45.3%**
  - Drug effect was dose-dependent
  - Post-hoc analysis: Absence of VOC episodes greater in patients treated with crizanlizumab vs placebo
    - 35.8% vs 16.9%
- **Adverse Reactions:** Most frequently reported adverse reactions (≥10%) in patients (N = 111) treated with 5 mg/kg crizanlizumab were back pain, nausea, pyrexia, and arthralgia
  - Severe (Grade 3) arthralgia and pyrexia rate of 0.9% (1 case each)

SCD, sickle cell disease; VOC, vaso-occlusive crisis.
Ataga et al. *N Engl J Med*. 2017;376:429-439; Kutlar et al. *Am J Hematol*. 2018; https://onlinelibrary.wiley.com/doi/abs/10.1002/ajh.25308

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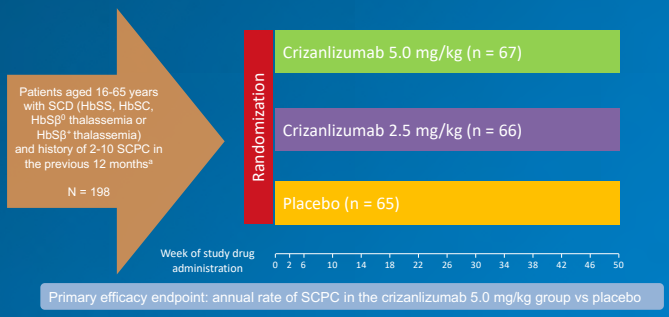
- The SUSTAIN trial examined crizanlizumab in individuals with sickle cell disease. This was a randomized, multicenter, phase 2, placebo-controlled, double-blinded trial which evaluated crizanlizumab, a monoclonal antibody to P-selectin.

SUSTAIN Trial: Study Design

A phase 2, multicenter, randomized, placebo-controlled, double-blind, 12-month study to assess safety and efficacy of crizanlizumab with or without hydroxyurea therapy in SCD patients with sickle cell–related pain crises



Primary efficacy endpoint: annual rate of SCPC in the crizanlizumab 5.0 mg/kg group vs placebo

[a]Patients receiving hydroxyurea or erythropoietin were included if prescribed for the preceding 6 months and dose was stable for ≥3 months.
SCD, sickle cell idsease; SCPC, sickle cell–related pain crisis.
Ataga et al. *N Engl J Med*. 2017;376(5):429-439.

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- The SUSTAIN trial examined high-dose crizanlizumab at 5 mg/kg, a middle dose of 2.5 mg/kg, and placebo and compared them over a 1-year period. The drug is given intravenously at week 0, week 2, and every 4 weeks. During the trial, this was carried out for an entire year. The primary efficacy endpoint was the annual rate of sickle cell–related pain crises in this trial.

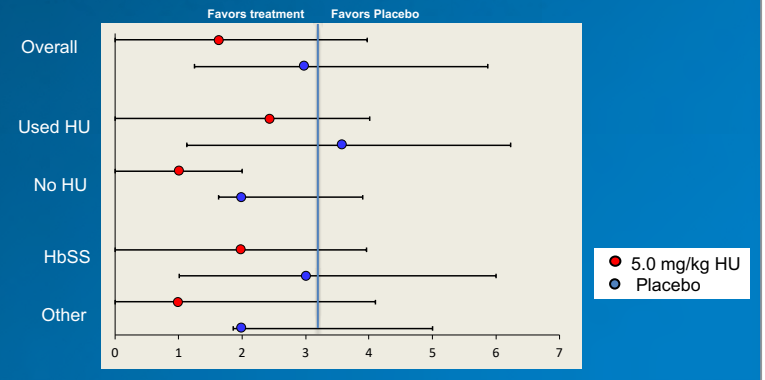
SUSTAIN Trial Summary

Endpoint	High-Dose Crizanlizumab, 5 mg/kg (N = 67)	Low-Dose Crizanlizumab, 2.5 mg/kg (N = 66)	Placebo (N = 65)
Annual rate of crises, ITT			
Median rate of crises/year	1.63	2.01	2.98
Difference from placebo (%)	-45.3	-32.6	-
P	.01	.18	-
No (%) of pts with crisis rate of 0 at end of trial	24 (36) >2-fold increase vs placebo	12 (18)	11 (17)
Median annual rate of days hospitalized/year	4.00	6.87	6.87
Difference from placebo (%)	-41.8	0.0	-
P	.45	.84	-
Median time to 1st sickle cell–related pain crisis (months)	4.07 Three-fold longer vs placebo	2.20	1.38
P	.001	.14	-
Median time to 2nd sickle cell–related pain crisis (months)	10.32	9.20	5.09
P	.02	.10	-

ITT, intention to treat.
Ataga et al. *N Engl J Med*. 2017;376:429-439.

- When we look at the results of the SUSTAIN trial, we found that we met the primary endpoint in the high-dose group in everyone regardless of whether they were receiving hydroxyurea or if they had hemoglobin SS disease or another genotype. So very exciting findings.

SUSTAIN Trial: Primary Endpoint Results Consistent Regardless of HU Use or HbSS Status



HU, hydroxyurea; VOC, vaso-occlusive crisis.
Adapted from Ataga et al. *N Engl J Med*. 2017;376:429-439.

Crizanlizumab-tmca: FDA Approval

- November 15, 2019: to reduce the frequency of VOCs in adults and pediatric patients aged 16 years and older with sickle cell disease
  - Recommended dose: 5 mg/kg intravenously over a period of 30 minutes on week 0, 2, and every 4 weeks thereafter
- Based on SUSTAIN trial
  - Primary efficacy outcome measure: annual rate of VOCs leading to a healthcare visit, defined as an acute episode of pain with no cause other than a vaso-occlusive event requiring a medical facility visit and oral or parenteral opioids, or parenteral NSAIDs
    - Voxelotor: 1.63 median annual rate of VOC
    - Placebo: 2.98 median annual rate of VOC
    - *P* = .010
- Most common adverse reactions (>10%): nausea, arthralgia, back pain, and pyrexia

NSAIDs, nonsteroidal anti-inflammatory drugs; VOCs, vaso-occlusive crises
FDA News Release. November 15, 2019.

AXIS Medical Education

- In November 2019, the FDA approved crizanlizumab to reduce the frequency of vaso-occlusive crises in adults and pediatric patients aged 16 years and older with sickle cell disease based on results of the SUSTAIN trial.

Clinical Trials Summary

Drug	Trial Name	Phase	Setting
Crizanlizumab (SEG101, SELG1)	SENTRY clinical trial program		
	SOLACE-adults NCT03264989	2	Pharmacokinetics and pharmacodynamics of crizanlizumab in SCD patients with VOC, ages 16 to 70 years
	SOLACE-kids NCT03474965	2	Dosing and safety of crizanlizumab, with or without hydroxyurea/hydroxycarbamide, in pediatric SCD patients with VOC, ages 6 months to 17 years
	STAND NCT03814746	3	Efficacy and safety of two doses of crizanlizumab (5.0 mg/kg and 7.5 mg/kg) vs. placebo, with or without hydroxyurea/hydroxycarbamide therapy, in adolescent and adult SCD patients with VOC, age 12 years and older
	SUSTAIN NCT01895361	2	Safety and efficacy of crizanlizumab with or without hydroxyurea therapy in SCD patients with sickle cell-related pain crises, ages 16 to 65 years • December 2018: Breakthrough Therapy designation for prevention of VOCs in patients of all genotypes with SCD • July 2019: Priority Review
	SUCCESSOR	retrospective cohort study	Subset of 48 adult patients, ages 18 or older, of the SUSTAIN placebo-controlled phase 2 trial, to evaluate SCD-related outcomes up to 52 weeks following trial completion; crizanlizumab was not administered in the 52 weeks post-SUSTAIN
Rivipansel (GMI-1070)	RESET NCT02187003	3	Efficacy and safety of rivipansel for the treatment of VOC in hospitalized patients with SCD, ages 6 years or older • Failed to reach both its primary endpoint (time to readiness-for-discharge after treatment) and secondary goals (time-to-discharge, need for opioids, time to discontinuation of opiods)
	NCT02433158	3 extension study	Safety of rivipansel in the treatment of one or more VOC in hospitalized subjects with SCD, ages 6 years or older
Voxelotor (GBT440)	NCT02850406	2	Pharmacokinetics, safety, tolerability, and exploratory treatment effect of GBT440 in pediatric participants with SCD, ages 4 to 17 years
	HOPE NCT03036813	3	Efficacy and safety of voxelotor compared with placebo in patients with SCD, ages 12 to 65 years • FDA Breakthrough Therapy, Fast Track, Orphan Drug and Rare Pediatric Disease designations for treatment of patients with SCD • September 2019: Priority Review
	034OLE NCT03573882	3 extension study	Effect of long-term treatment with voxelotor in participants who have completed treatment in HOPE study

SCD, sickle cell disease; VOC, vaso-occlusive crisis.

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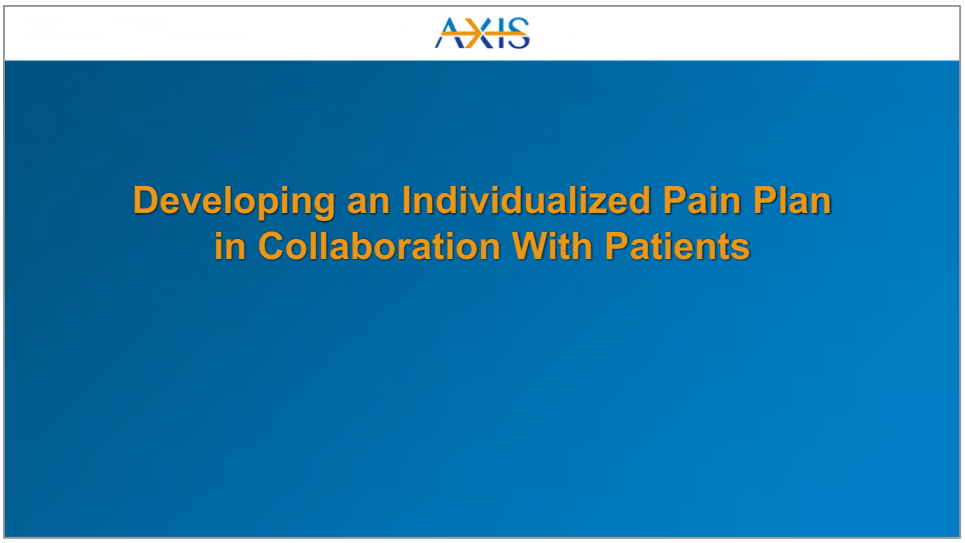
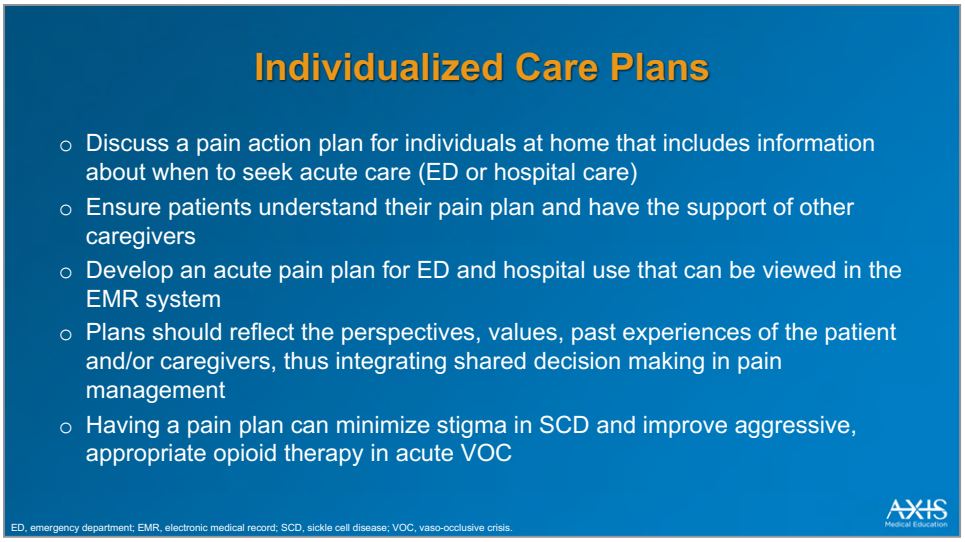
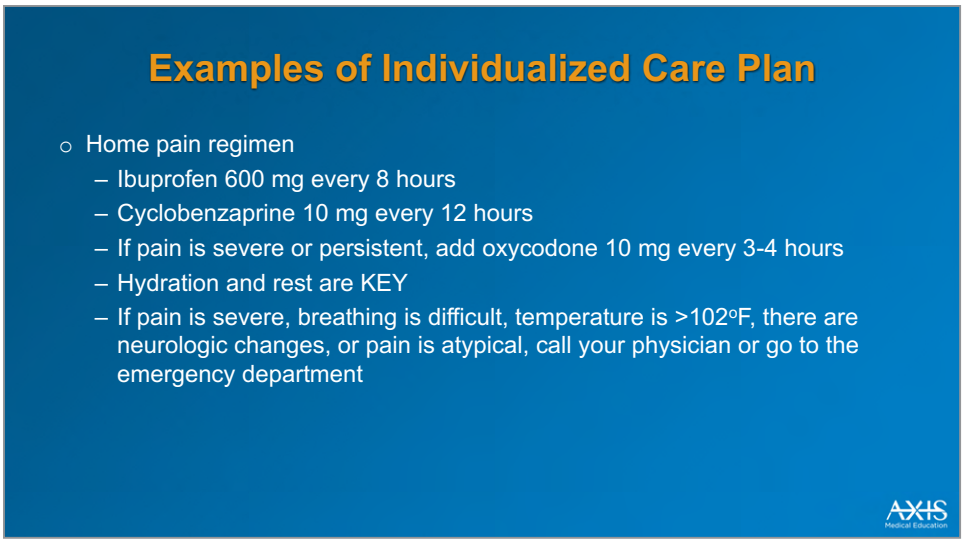
- There are multiple clinical trials that have been looked at using crizanlizumab, using a similar pan-selectin inhibitor called rivipansel or GMI-1070, and the voxelotor trials that we've already reviewed.



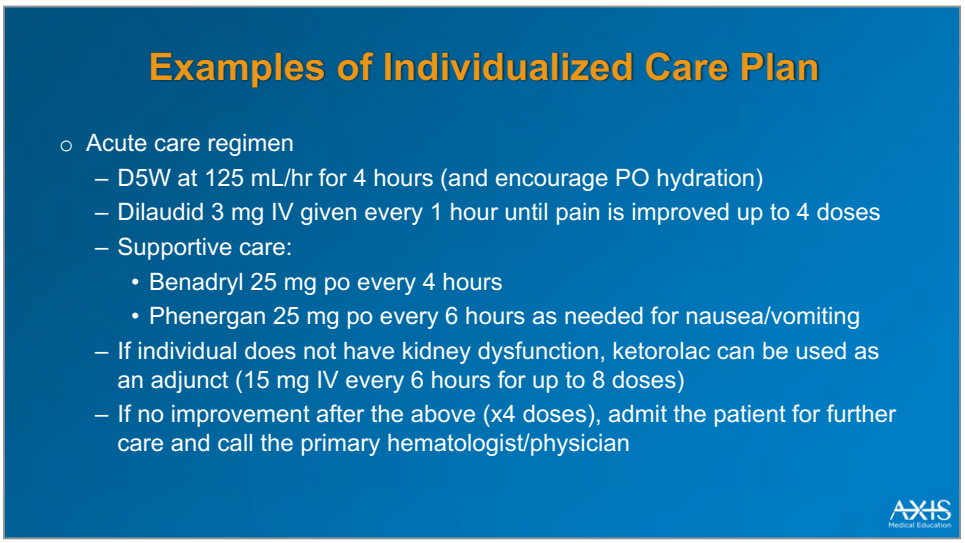
- Finally, let's talk about how we develop individualized plans for our patients. Dr. Ogunsile, can you tell us how to develop these individualized pain plans with our patients?



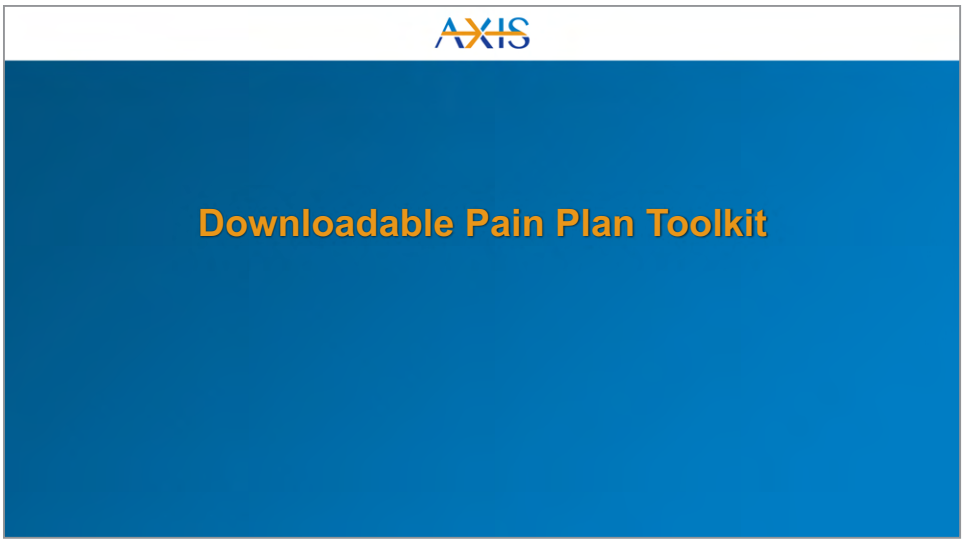
- **Ogunsile:** Let's transition to developing an individualized pain plan in collaboration with patients. It's important to discuss a pain plan with individuals that includes information to manage pain at home and of when to seek care. It's important to have the viewpoints of other caregivers, and that the pain plan is readily available in the electronic medical record system for other physicians and providers to view. The pain plan should reflect the perspectives, values, and experiences of the patient and/or caregivers, and essentially is a shared decision-making plan. Having a pain plan can minimize stigma in sickle cell disease and improve aggressive, appropriate opioid therapy in acute VOCs.



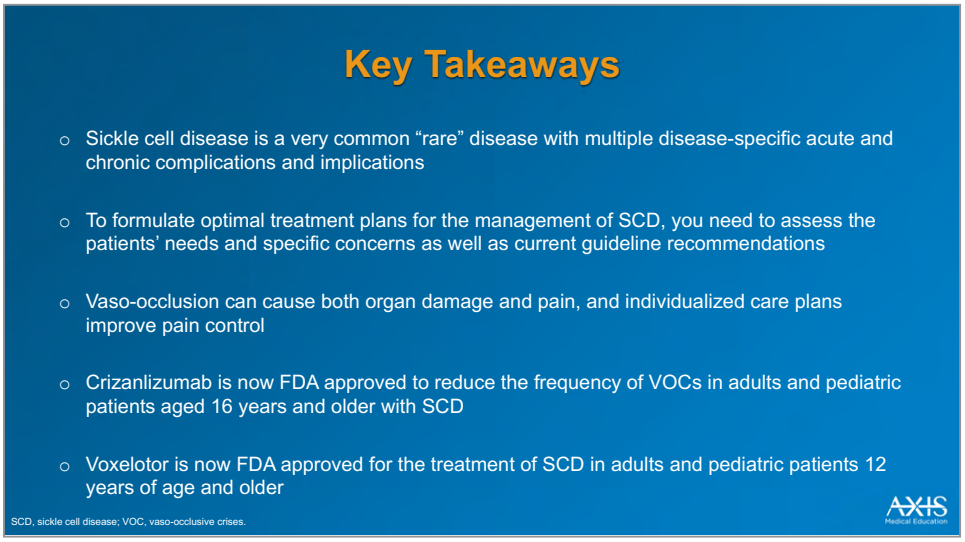
- Here are some examples of an individualized care plan. At home, the patient is advised to take ibuprofen 600 mg every 8 hours, cyclobenzaprine 10 mg every 12 hours. However, if the pain is severe or persistent, we'll ask the patient to add oxycodone 10 mg every 3 to 4 hours. We stress to the patient that hydration and rest are key. Then, if pain is severe or if breathing is difficult or if they have a fever or neurologic changes—any red flags at all—we ask the patient to call the physician or go the emergency department.



- In an acute setting, we ask that patients receive IV fluids, IV pain medications, along with supportive care. And if the patient has adequate renal function, we also add IV ketorolac as an adjunct. If there is no improvement in their pain after all of these managements, then we should admit the patient for further care and call the primary hematologist or physician.

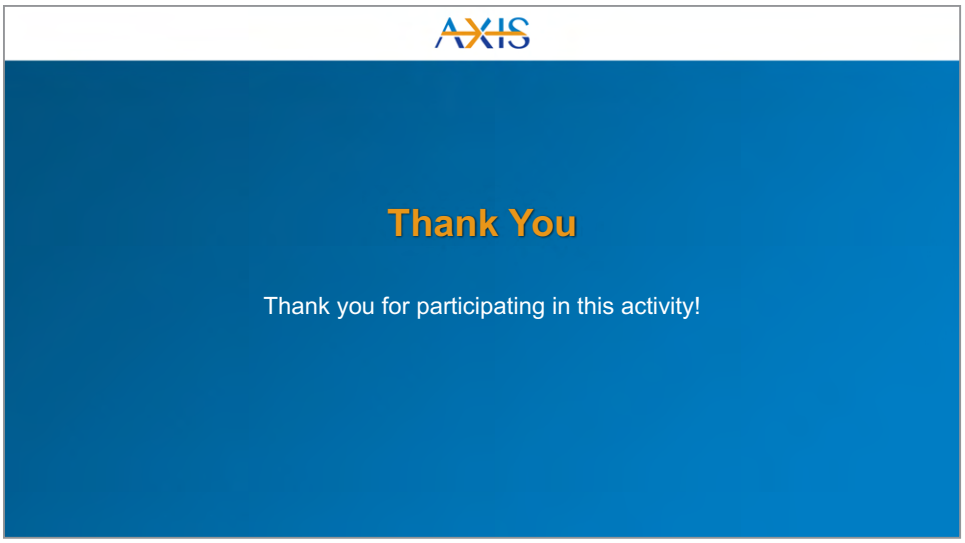


- There is a pain plan toolkit, provided by AXIS, which may be helpful in this scenario.



- **Kanter:** Thank you so much for discussing this exciting data with me today. Dr. Ogunsile, it is really important that we understand how to use these individualized care plans and provide the best team-based care for our patients. I'm certainly excited that our audience has been able to join us in this activity today.

  Let's review some key take-aways. Our conclusions today are that sickle cell disease is a common "rare" disease with multiple disease-specific acute and chronic complications. We need to formulate optimal treatment plans to manage individuals living with sickle cell, assess patients' needs and their concerns, and be aware of current guideline recommendations. Together, we can then make an adequate treatment plan for an affected individual. Vaso-occlusion can cause both organ damage and pain. Again, individualized care plans are incredibly important. There are several new therapies in development and on the horizon in sickle cell disease. Team-based care and access to a hematologist remain as cornerstones of care.



- Dr. Ogunsile, thank you, again, for joining me in this activity today.

  Ogunsile: Thank you, Dr. Kanter, for having me.

  Kanter: Thank you to the audience for your participation, as well.

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