(PLEASE NOTE: Transcribed automatically by Vimeo, mistakes are possible/likely. Our apologies.)

TRANSCRIPT - GR 02 25 22 "Sickle Cell Disease: Advances in Management " ***Kelly Davidson, MD,*** **from the University of Virginia**

Izzy Budnick

00:19:32Okay all right everyone, welcome to grand rounds.

- 00:19:36Today we are going to have a presentation from Dr Davidson but before we get started.
- 00:19:42um you know we'd like to honor the legacy of Dr Paul Farmer and the world renowned anthropologists and physician who passed away this Monday at the age of 60 to.
- 00:19:52Our offices had numerous faculty combined to talk about the impact of this man's life.
- 00:19:56on their work, and I know his impact is difficult to quantify given the breadth and depth of his accomplishments everyone, I gather, was a person with an immense reserve of efficacy of kindness.
- 00:20:06Before having a moment of silence i'll leave this up one of his quotes he said that the essence of global health equity is the idea that something so precious this House might be viewed as the right.
- 00:20:37Okay.
- 00:20:39Alright, so now, I have the pleasure of introducing our grammar and speaker for today, Dr Kelly Davidson from our own division of hematology and oncology.
- 00:20:47Dr Davidson is a graduate of the Washington university school of medicine and a graduate of the internal medicine residency at Beth Israel deaconess medical Center.
- 00:20:55Dr Davidson served as the chief residents of the West West Roxbury VA medical Center and then came down to uva to complete her hematology and oncology fellowship after starting.
- 00:21:06After several years of practice in Rockville Maryland Dr Davidson return to do a full to join the division of hematology and oncology in 2009.
- 00:21:14And it's interesting to the academic rank of associate professor of medicine.
- 00:21:17Dr Davidson attends and the impatient metallic console service on the console service.
- 00:21:22And in the outpatient hematology clinics, where particular she is responsible for a comprehensive clinic for adults with sickle cell disease.
- 00:21:29Dr Davidson has research interests and electronic consultation, if you mythology and the treatment and biology of sickle cell disease.
- 00:21:36Dr Davidson has and continues to serve and numerous roles within the health system, including on the medicine service lines.
- 00:21:42home team sickle cell disease steering committee as the Chair of the iron and pregnancy-working group that's the top notch Decatur students residents and fellows here at uva.

- 00:21:52and recognition of the comprehensive care of that she delivers to the order both to Charles l brown Award for patient care, quality and the Department of medicine Award for clinical excellence in 2009.
- 00:22:02Today, Dr Davidson will give it an important update on the management of sickle cell disease, Dr Davidson, the floor is yours.

Kelly Davidson

00:22:13Thank you very much me share my screen.

- 00:22:22Right, can you all see that.

Unknown Speaker

00:22:25Yes.

Kelly Davidson

00:22:30Well, thank you very much for that introduction and for the opportunity to speak with you all today about sickle cell disease advances in management.

- 00:22:39These are my disclosures.
- 00:22:43Today, I will describe the complex pathophysiology of sickle cell disease, with a focus on potential targets for therapeutic intervention.
- 00:22:50We will then review the for currently approved disease modifying therapies for sickle cell disease and, finally, we will explore curative approaches for sickle cell disease.
- 00:23:01sickle cell disease first appeared in western literature in Chicago in 1910 when Dr James Harris described a case of severe Malays and anemia and a 20-year-old dental students from Grenada.
- 00:23:12and examining his blood smear he noticed many bizarrely shaped red blood cells leading him to surmise that quote the cause of the disease, maybe some unrecognized change in the red car possible itself.
- 00:23:25sickles cell disease was the first demonstration of a disease due to an abnormal protein.
- 00:23:30In 1949 Linus Pauling and colleagues use the newly invented technique of protein elector freezes.
- 00:23:36To demonstrate that sickle hemoglobin and normal hemoglobin have different electromagnetic properties; they were the first to describe this as a molecular disease.
- 00:23:45In 1956 Dr Vernon Ingram building on these discoveries elucidated the biochemical explanation by showing that the substitution of new tannic acid with veiling in the beta global chain of hemoglobin.
- 00:23:57accounts for the unique shape of the affected red blood cells and their sensitivity to low option states.

- 00:24:03In the 1970s, using recombinant DNA technology scientists found the nucleotide change in the DNA for sickle hemoglobin results from an admin to timing substitution at code on six of the beta globe and gene on chromosome 11.
- 00:24:17sickle cell anemia was the first human disease to be explained at the level of a single nucleotide mutation and it is one of the most common monogenic disorders in the world.
- 00:24:27Even though the underlying molecular cause of the disease was understood more than half a century ago, progress in translating this knowledge and to improve patient care has been slow.
- 00:24:38hemoglobin is a Tetra americ protein composed of different combinations of globe and sub units each globe and sub unit is associated with the Co factor team which can carry a molecule of oxygen.
- 00:24:49Several genes in code different types of globe and proteins and their various Tetra americ combinations generate multiple types of hemoglobin.
- 00:24:56which are normally expressed at different stages of life embryonic fetal and adult hemoglobin a is the most abundant form of adult hemoglobin.
- 00:25:05is comprised of two alpha globe and sub units and to beta globe and subunits the top diagram describes an individual who has to normal beta global genes and produces only hemoglobin a.
- 00:25:17The second diagram demonstrates an individual with sickle cell trait with one normal beta globe and gene, and one with the beta so.
- 00:25:24This is not a disease and most people with sickle cell trait will have no symptoms and will not have any health complications related to their sickle cell trait.
- 00:25:33sickle cell disease is an umbrella term that includes several genotypes the bottom three diagrams represent the most common genotypes.
- 00:25:41A person who is homozygous for the hemoglobin s mutation has SS disease or sickle cell anemia.
- 00:25:47and sickle cell anemia the intracellular concentration of hemoglobin so it's almost 100%, this is the most severe phenotype and the majority of the therapeutic developments and interventions are focused on this.
- 00:25:59Other affected individuals may have one copy of hemoglobin s and another mutated beta globe and gene that produces a different abnormal hemoglobin such as hemoglobin C.
- 00:26:08or a quantitatively deficient hemoglobin in the case of a beta fallacy me a mutation patients who are compound header zygote may have milder phenotypes but still can have a debilitating clinical course.
- 00:26:21under conditions of the oxygenation that is when the hemoglobin is not bound to oxygen.
- 00:26:25hemoglobin touch rumors that include to have these mutant sickle beta globe and subunits can polarize and cause the earth or sites to assume a crescent or circle shape.
- 00:26:34These red cells become inflexible, resulting in humility anemia and blockage of blood flow they're also more susceptible to endothelial adhesion.
- 00:26:45sickle cell disease is a huge global health problem and is the most commonly inherited blood disorder in the world.
- 00:26:51It is estimated that 300 to 400,000 babies with sickle cell disease are born, each year, the majority in sub Saharan Africa.

- 00:26:59Approximately 100,000 Americans are affected, and more than 20 million people worldwide have sickle cell disease on the right is a map showing the estimated numbers of births with sickle cell anemia per 100,000 births per country in 2015.
- 00:27:13sickle cell disease is prevalent in regions where malaria was historically endemic, including sub Saharan Africa, India, the Middle East and the Mediterranean.
- 00:27:22This is because people with sickle cell trait are protected against severe plasmodium falciparum malaria.
- 00:27:27Unfortunately, the majority of children in Africa with sickle cell disease will die within the first five years of life of preventable causes often before a diagnosis is even made.
- 00:27:37In many areas, there are no newborn screening programs this and the lack of basic healthcare infrastructure in many regions, makes the prevention and management of sickle cell disease extremely challenging in many parts of the world.
- 00:27:49In the United States since 2007 all states have had universal screening programs at birth for sickle cell disease.
- 00:27:55In the US, due to the implementation of multiple interventions, including newborn screening immunizations use of prophylactic antibiotics and use of hydroxyurea.
- 00:28:05Over 95% of children survive to be adults, however, overall survival still lags 20 to 30 years behind that of a non-sickle cell disease patient.
- 00:28:17Although it is caused by a single misinterpretation sickle cell disease is a complex, multi system condition characterized by acute and chronic complications affecting virtually every organ system.
- 00:28:28A kid complications bring the individual with sickle cell disease to immediate medical attention the most common of which is pain database inclusive crisis.
- 00:28:36Patients also commonly present acutely due to infections acute test syndrome splint sequestration priapism compatibility complications and stroke.
- 00:28:46As individuals with sickle cell disease age chronic complications lead to organ dysfunction that contribute to morbidity and mortality, these include chronic pain sickle nephropathy pulmonary hypertension, a vascular necrosis retinopathy and heart failure.
- 00:29:04based on current evidence the pathophysiology of sickle cell disease is considered to be a vicious cycle of four major processes all the subject of active study and novel therapeutic targeting.
- 00:29:14shown in a the fundamental event that underlies the complex pathophysiology and multi system at consequences of sickle cell disease is a polymerization of hemoglobin so that occurs under low oxygen tension.
- 00:29:26polarization of the D oxygenated hemoglobin s alters the structure and function of the red blood cells.
- 00:29:31These damaged director sites are not only less flexible compared to normal earth or sites, but also highly adhesive.
- 00:29:38aggregation of sickle directory sites with neutrophils platelets and endothelial cells, promote status of blood flow leading today's occlusion as shown in be.
- 00:29:47Phase occlusion then promote a scheme yet reperfusion injury repeated cycles of cycling and unsettling shortens the lifespan of the damage red cells to about one six out of normal red cells.

- 00:29:59Analysis of these damage red cells releases cell free hemoglobin into the circulation, as shown and see which promotes endothelial dysfunction by depleting nitric oxide reserves and leading to oxygen free radical formation.
- 00:30:12More recently, it has been described that sterile inflammation plays an important role in the pathophysiology of sickle cell disease, as shown in D.
- 00:30:19cell free hemoglobin and ischemia reperfusion injury contribute to sterile inflammation by activating the inflammatory pathway and vascular and inflammatory cells.
- 00:30:29leading to production of inflammatory cytokines and further promoting and he's ignis of neutrophils platelets and endothelial cells these molecular cellular and biophysical processes Center dies to promote acute and chronic pain and an organ damage and sickle cell disease.
- 00:30:48There are a number of current and future therapies targeting different aspects of the molecular pathophysiology of sickle cell disease.
- 00:30:54In a we have drugs that are capable of modulating hemoglobin polymerization earth recite dehydration and hemoglobin oxygen affinity.
- 00:31:03nb we have drugs that are capable of preventing bazell occlusion by inhibiting adhesive interactions between white cells platelets or endothelial cells and earth recites.
- 00:31:12and see we have drugs that can prevent and affiliate dysfunction by scavenging hemoglobin and reactive oxygen species or promoting nitric oxide synthesis.
- 00:31:21And indeed, we have drugs that are capable of preventing sterile inflammation by various mechanisms, including scavenging him and reactive oxygen species and inhibiting inflammatory activation I've highlighted the for disease modifying agents that we will review during this talk.
- 00:31:38I wanted to start with a case to frame our discussion, so this is the 23-year-old female with hemoglobin SS disease, who presents for follow up.
- 00:31:45Since her last visit, three months ago she has had one admission and to er visits for vasopressin crisis.
- 00:31:51She has to prior episodes of acute chest syndrome and several red cell aloe antibodies her baseline hemoglobin is around eight grams per deciliter.
- 00:32:00she's prescribed hydroxyurea 1500 milligrams daily folic acid, and she takes ibuprofen and hydromorphone prn two reports that she has not taken her hydroxyurea for several months to fear of side effects, she wants to know what she can do to reduce the frequency of pain crisis.
- 00:32:19So I first wanted to start with a review of hydroxyurea, this is an old drug and has been around and use for decades it inhibits ribonucleic cyber duck days and was first approved in the 1960s, as an Antonio plastic agent.
- 00:32:31hemoglobin F or fetal hemoglobin is the main auction carrier in the human fetus through early infancy reaching less than 1% of total hemoglobin in normal individuals by age one.
- 00:32:42It is composed of two alpha globe and to gamma globe and subunits and thereby lacks any beta globe and chains.
- 00:32:48In vitro hemoglobin APP has been shown to inhibit suckling by interfering with the polymerization of hemoglobin ass.

- 00:32:55hydroxyurea is known to increase hemoglobin F levels, so the exact mechanisms for hemoglobin F induction remain in completely understood.
- 00:33:03The induction of hemoglobin F is likely, the main benefit and sickle cell disease hydroxyurea has a number of other effects, as shown in the graphic on the right.
- 00:33:11To it is marrow suppressive and this lowers neutrophils and ridiculous eight counts, it has been shown that an elevated white count is associated with morbidity and mortality and sickle cell disease.
- 00:33:21It also decreases and he's Agnes and improves the reality of circulating neutrophils and particular sites.
- 00:33:27It reduces analysis through improved earth recite hydration macro psychosis and reduced intracellular signaling and finally it acts as a nitric oxide donor, leading to local visitation and an improved vascular response.
- 00:33:42The 1995 msha trial was a pivotal study looking at hydroxyurea and sickle cell disease.
- 00:33:48This was a randomized double blind placebo controlled clinical trial to test the hypothesis that hydroxyurea could substantially reduce the frequency of VOC and adults with sickle cell anemia.
- 00:33:58It was conducted at 21 sites in the US and Canada 299 patients with hemoglobin SS disease and three or more VOC per year were enrolled.
- 00:34:07Other gina types were excluded other exclusion criteria included pregnancy chronic transfusion program history of stroke, in the last six years and HIV infection.
- 00:34:17Patients are randomized either hydroxyurea or placebo hydroxyurea was tight rated to maximum tolerated dose based on cell counts, starting at a dose of 15 milligrams per day.
- 00:34:28The study was planned for two years and the primary outcome was a number of painful crises.
- 00:34:33Painful crises were defined as visits to a medical facility lasting more than four hours and resulting in treatment with a parental narcotic acute chest syndrome priapism and hepatic sequestration were also included in this definition.
- 00:34:48There were no significant differences between the two groups of patients, their respective sex, age, race or ethnic group.
- 00:34:54Both have similar rates of complications of sickle cell disease and baseline blood counts and the two groups were similar before Truman was initiated.
- 00:35:02baseline hemoglobin F levels were around 5% in both arms because of the beneficial effects observe the trial was stopped early before the plan 24 months of treatment were completed.
- 00:35:13The annual rate of painful crises different significantly in the two treatment groups with a median rate of 2.5 crises per year in the hydroxyurea arm compared to 4.5 crises per year and the placebo group.
- 00:35:25This represents a 44% difference in the annual rate of pain crisis when only crises severe enough to cause hospitalization or considered the median annual rates for 1.0 and 2.4 respectively.
- 00:35:37There was also a significant reduction in the rates of acute test syndrome and transfusion requirements, the incidence of death stroke and hepatic sequestration did not differ significantly in the two groups.

- 00:35:51As shown in the two graphs on the left the median time to both the first and second base inclusive crisis was significantly longer and patients treated with hydroxyurea that in those given placebo.
- 00:36:01effect was evident in less than six months there were two deaths in the hydroxyurea regroup and five and the placebo arm, none of the deaths were felt to be related to treat my with hydroxyurea.
- 00:36:12There has been concerned that long-term hydroxyurea use maybe carcinogenic or leukemia genetic because some other Antonio plastic agents do have such effects.
- 00:36:21noni a plastic disorders developed during the study treatment was temporarily stopped and almost all patients in the hydroxyurea group because of marrow suppression blood counts, usually recovered within two weeks, only two patients stop hydroxyurea permanently due to my list depression.
- 00:36:38pregnancies occurred in 10 patients or their partners and therapy was stopped in all cases, all life born babies appear to be normal.
- 00:36:46hair loss rash fever and gastrointestinal symptoms, whereas common and patients receiving placebo, as in those taking hydroxyurea.
- 00:36:54Based on the positive results from the study hydroxyurea was approved by the FDA in 1998 for adults to sickle cell anemia and in 2017 the approval was extended for use and pediatric patients.
- 00:37:09The 299 individuals enrolled in the MSA trial have been followed over time.
- 00:37:14Many of those who originally assigned to placebo were subsequently switched to hydroxyurea after the short term benefits of Hydra had become apparent.
- 00:37:22This is data from a 2010 observational study that reported the long-term outcomes of the patients from the original msha trial.
- 00:37:29They were followed for greater than 17 years and what we see is a significant reduction in deaths with long-term hydroxyurea exposure.
- 00:37:37Although the death rate in the overall cohort was high at 43% mortality was reduced and individuals with long-term exposure to hydroxyurea.
- 00:37:46The graph demonstrates the cumulative mortality during the fsh follow up by cumulative hydroxyurea exposure.
- 00:37:5287% of the deaths occurred and individuals who are either never exposed to hurt to hydroxyurea or who had less than five years of exposure rates of stroke organ dysfunction infection a malignancy are similar in all groups.
- 00:38:08hydroxyurea is associated with decreased rates of VOC acute test syndrome hospitalization transfusion stroke and has a survival advantage in sickle cell disease.
- 00:38:18Responses can take three to six months I always explain this to patients the drug is not meant to treatment acute pain crisis and it should not first be initiated during intermission for pain crisis.
- 00:38:28We want patients to establish outpatient follow up in order to discuss the risks and benefits.
- 00:38:33The typical starting dose is 15 milligrams per kilogram daily with adjustments every six to 12 weeks to a maximum dose of 35 minutes per kid per day or mtd.

- 00:38:43hydroxyurea can be continued during a routine admission for bazell clues of crisis unless the patient has a significant aka I developed side opinions are there is concerned, for a plastic crisis.
- 00:38:55Most of the data supporting the use of hydroxyurea is in the hemoglobin SS genotype it's used in other genotypes should be individualized and based on disease severity.
- 00:39:05Patients with non-SS genotypes often have a milder phenotype, but I do consider hydroxyurea if these patients have more severe manifestations.
- 00:39:14hydroxyurea may be given with other disease modifying therapies and it should be held during attempts at conception, both male and female, and during pregnancy or lactation.
- 00:39:24Given the benefits of hydroxyurea is important to address the many potential barriers to its use both on patient and provider issues, there is often hesitancy among providers about the safety and efficacy of hydroxyurea.
- 00:39:37And patients may have concerns about person engineer city to city fertility risks and other side effects, as well as trouble complying with daily dosing or adhering to the frequent clinical and laboratory monitoring is required.
- 00:39:52So what about l glutamine.
- 00:39:54Well, an ad is a redux co-factor and red cells and plays a role in maintaining redux balance, we know that oxidative stress contributes to the pathophysiology of sickle cell disease.
- 00:40:04So medications that aim to reduce the stress may have therapeutic benefits l glutamine is a conditionally essential amino acid.
- 00:40:12I one for which increased levels are needed in certain conditions such as stress and it is required to synthesize and add in earth recite.
- 00:40:20By improving the nav to nadh intracellular ratio of glutamine enhances the redux potential within the red cells and reduces oxidative stress.
- 00:40:29uptake of L glutamine is several times greater and sickle red cells than normal red cells primarily to increase the total intracellular energy level.
- 00:40:38Based on these potential benefits investigators conducted a randomized placebo controlled double blind parallel group trial at 31 sites across the United States.
- 00:40:47This is the only phase three trial avail glutamine and sickle cell disease.
- 00:40:51230 patients ages five and older with hemoglobin SS or sickle beta zero fallacy MIA who had two or more of a zero Plus of crises in the past year.
- 00:41:00or randomized in a two to one fashion to receive either l glutamine at a dose of 0.3 grams per kilo pov ID or placebo for 48 weeks.
- 00:41:10Patients who are receiving hydroxyurea at stable doses were allowed to continue therapy patients with recent transfusions renal insufficiency uncontrolled liver disease pregnancy and lactation were excluded.
- 00:41:22The primary endpoint was the number of sickle cell crises, a composite of painful events acute stress syndrome acute chronic sequestration and priapism.
- 00:41:31Secondary endpoints included the number of hospitalizations and er visits for sickle cell related pain and changes and hematologic measures from baseline through week 48.
- 00:41:43baseline characteristics were well matched in both arms the age range was five to 58 and two thirds of the patients were on concurrent hydroxyurea.

- 00:41:53Most patients had hemoglobin SS disease, with a minority having sickle beta fallacy MIA most had to defeat five pain crises per year and baseline hemoglobin was around 8.7 to 8.8.
- 00:42:07On the right is an analysis of recurrent sickle cell related pain crises plotted over time, according to trial group.
- 00:42:13This yielded and intensity ratio of 0.75 which indicates that the cumulative number of pain crises was 25% lower in the l glutamine group as compared to the placebo group during the 48-week treatment period.
- 00:42:30In terms of the primary endpoint the number of pain crises was significantly reduced with a meeting of three in the glutamine arm versus four and the placebo arm.
- 00:42:38In terms of secondary endpoints hospitalizations were reduced by 33% with a median of two in the glutamine group versus three in placebo.
- 00:42:47A number of ED visits for sickle cell pain did not differ significantly between the trial groups, however, the media number of days in hospital was reduced from 11 to 6.5.
- 00:42:58And the median time to first and second pain crises was reduced was longer in the treated group versus placebo, there were also your episodes of acute test syndrome.
- 00:43:08not shown in the table, but there was no significant between group difference in the change in hemoglobin level to management level or ridiculous account.
- 00:43:16This is of note, since the purported mechanism of L glutamine is a reduction in oxidative stress which theoretically should reduce analysis.
- 00:43:24results for similar regardless of concurrent hydroxyurea therapy the rates of adverse events were actually hiring the placebo group than the glutamine group at 100% versus 98%.
- 00:43:35Patients taking glutamine had more frequent nausea non-cardiac chest pain fatigue and musculoskeletal pain.
- 00:43:42There were two deaths and L glutamine group both patients in their mid 40s and these deaths were not felt to be related to the study drug there was a high dropout rate in this phase three study 36% without glutamine and 24% with placebo.
- 00:43:59So almost 20 years after hydroxyurea was approved in 1998 we finally had a second drug to treat sickle cell disease.
- 00:44:06The high dropout rate and the only phase three study makes it somewhat difficult to interpret the results, and we really do not know exactly how this works.
- 00:44:13In sickle cell disease, but the FDA felt it had a favorable risk to benefit profile and approved out glutamine or and dari in 2017 for patients five and older with sickle cell.
- 00:44:23disease to reduce the frequency of acute pain crisis.
- 00:44:28There have been some concerns raised about increased mortality with l glutamine use among critically ill patients.
- 00:44:33Based on a study in the New England journal from 2013 that looked at the use of L glutamine and antioxidants in a critically ill population of patients, not those with sickle cell disease.
- 00:44:43So close monitoring is recommended, when used in patients who are at risk for multi organ failure are those with renal or hepatic impairment.
- 00:44:50The drug comes in five grand packets of powder and the dose is 123 packets PO twice daily and its weight based dosing.

- 00:44:57The drugs should be mixed in a room temperature or cold liquid or food not hot as the drug is heat label.
- 00:45:03Use the pharmacologic grade glutamine is recommended over the counter formulations of glutamine should probably be avoided as the purity of the supplements is unclear and less regulated.
- 00:45:13There is no therapeutic Drug Monitoring that is required, and it is reasonable to add glutamine to hydroxyurea therapy and patients who continue to have pain, despite adequate doses of hydroxyurea or if hydroxyurea is poorly tolerated.
- 00:45:27Long term efficacy data are lacking with this drug and is about 20 times more expensive than hydroxyurea.
- 00:45:35So back to our case you discussed the risks and benefits of hydroxyurea and she agrees to resume.
- 00:45:41The frequency of admissions is improved, after several months on hydroxyurea but she continues to have episodes of acute pain requiring occasional er and infusion Center visits she wants to try glutamine.
- 00:45:52Insurance initially declined a glutamine but, ultimately, she was able to obtain the drug unfortunately she develops nausea and bloating and elects to discontinue.
- 00:46:02What else can you recommend to help reduce praise reclusive crisis.
- 00:46:07Although polymerization of D oxygenated hemoglobin s is the primary event in the pathophysiology of sickle cell disease.
- 00:46:14The pathogenesis of occlusion is complex base occlusion is caused by the adhesion of sickle earth recite and leukocytes to the endothelial which results in vascular obstruction and tissue ischemia.
- 00:46:25In addition, platelets can bind to earth recites mana sites and neutrophils to form aggregates which contribute to abnormalities of blood flow and patients with sickle cell disease.
- 00:46:35He should have leukocytes to the endothelial during inflammation involves multiple molecules but the process is initiated by piece selected.
- 00:46:43piece of leptin is found in storage granules of resting endothelial cells and platelets and is rapidly transferred to the cell membrane on activation of the cell during processes such as inflammation.
- 00:46:53The regulation of P select and endothelial cells and platelets contributes to the cell cell interactions they're involved in the pathogenesis of babies occlusion and sickle cell related pain crises.
- 00:47:04Prison lissa map is a humanized monoclonal antibodies that binds to be selected and blocks its interaction the piece electing like a protein leg and one is shown in the cartoon on the right.
- 00:47:15This is Dane trial was a double blind randomized placebo controlled face to trial of Christian was a map and sickle cell disease was conducted at 60 sites in the US, Brazil and Jamaica.
- 00:47:26198 patients were enrolled including all sickle cell gina types patients ages 16 to 65 were included and had experienced two to 10 days inclusive crises in the year prior to enrollment.

- 00:47:38Patients were randomized in a one to one to one fashion to hide host kristin let's map low dose Christian was a map or placebo.
- 00:47:46The drug was given intravenously over 30 minutes at weeks 02 and then every four weeks for a year, patients on a stable dose of hydroxyurea were included.
- 00:47:55The trial excluded those on chronic red cell exchange chronic transfusion or chronic anticoagulation other than aspirin.
- 00:48:03The primary outcome was the annual rate of pain crises with high dose prison was an APP versus placebo.
- 00:48:08sickle cell related pain crises were defined as acute episodes of pain database occlusion and requiring treatment in a medical facility.
- 00:48:16acute chest hepatic and splint sequestration and priapism were also considered crisis events.
- 00:48:21Secondary endpoints included days hospitalized time to first and second crisis annual rates of uncomplicated crisis and rates of acute chest patient reported outcomes using pain severity scores were also assessed.
- 00:48:38The three groups were generally well matched there was a slightly younger population of placebo arm about 70% of patients had hemoglobin SS disease and two thirds were taking concurrent hydroxyurea most had on average two to four crises in the year prior to enrollment.
- 00:48:55And the intention to treat analysis, the media and crisis rate per year was 1.63 in the high dose presenteeism ad group.
- 00:49:01as compared with 2.98 and the placebo group indicating a 45.3 lower rate of pain crises with high dose crystals a map this difference was statistically significant.
- 00:49:12The median crisis rate per year and the low dose group was 2.01 which was 32.6% lower but this did not meet statistical significance.
- 00:49:21The median time to first crisis was significantly longer among patients receiving high dose prison was a map than those receiving placebo, as was the median time to the second crisis.
- 00:49:32In terms of other secondary endpoints there was a trend toward a reduction in the rate of days hospitalized with high dose Christian was a map versus placebo, but the difference was not significant.
- 00:49:41The annual rate of uncomplicated pain crisis was significantly lower in the high dose group versus placebo, with a median of 1.08 per year versus 2.91.
- 00:49:51In this trial, the acute chest syndrome, the paddock sequestration splint sequestration and priapism were rare events and there were no significant differences between either of the active treatment groups and the placebo group.
- 00:50:03On the right, we have the kaplan Meier curve, so the median time to first and second sickle cell related pain crisis according to trial group.
- 00:50:09High dose Christian lizard magazine yellow and placebo and green.
- 00:50:13The lower crisis frequency seen with the high dose Christian lizard map was evident within two weeks after the start of the 52-week treatment phase and was maintained throughout the study period.

- 00:50:23There were no significant differences in measures of homelessness no significant change in pain severity scores and results were similar regardless of concurrent hydroxyurea use or underlying sickle cell gina type.
- 00:50:36serious adverse events were reported and 55 patients, including 17 in the high dose group 21 in the low dose group and 17 with placebo.
- 00:50:46The serious adverse events that occurred and at least two patients and either active treatment group and at a higher frequency than placebo or pyrex yeah and influence up.
- 00:50:56There was one serious bleeding event an episode of intracranial hemorrhage in a patient in the low dose kristin kristin was a map group.
- 00:51:03The patient was also being treated with control act which is associated with an increased risk of hemorrhagic stroke.
- 00:51:09No other clinically significant bleeding events were observed adverse events that occurred in 10% or more of the patients and either active treatment group.
- 00:51:17or headache back pain nausea arthralgia musculoskeletal pain, as well as others listed in the table, there were five desk during the study and none were felt to be related to the study drug.
- 00:51:30Based on the results from the sustain child the peace selected inhibitor Christian was a map or a Doc do was FDA approved in November 2019.
- 00:51:39For patients age 16 and older with sickle cell disease to reduce the frequency of a zero Plus of crisis.
- 00:51:45The standard dose is five milligrams per kilogram intravenously given over 30 minutes at week zero and two followed by every four weeks, and it can be given, with or without hydroxyurea.
- 00:51:56Prison was a mad maybe a good option for individuals who have difficulty with adherence to oral medication and those who are able to tolerate monthly intravenous therapy.
- 00:52:05For some, the need for monthly clinic visits for the infusion maybe an obstacle to use IV access can also be an issue, particularly as patients age.
- 00:52:14Common side effects include arthralgia nausea and rare infusion reactions, the drug may also cause platelet clumping, particularly when the CBC is collected in an ETA 10 containing two, which is a purple top to cost may be a barrier for some patients.
- 00:52:32After reviewing the data with your patient she agrees to a trial of prison was a map, in addition to continuing hydroxyurea.
- 00:52:38She tolerates therapy well and notes a reduction in the frequency of pain episodes six months later, she is admitted with a pain crisis in the setting of pneumonia.
- 00:52:47She requires a blood transfusion and unfortunately this is complicated by hyperkinetic transfusion reaction she sees you and follow up and wants to know if there's anything else you can do to improve her.
- 00:53:01hemoglobin s polymerization is the initial triggering event and sickle cell disease.
- 00:53:05Because the rate of hemoglobin s polymerization is extremely sensitive to D oxygenated hemoglobin so concentration small changes and concentration can have substantial effects on polymerization.

- 00:53:17box ella tour is an orally bioavailable small molecule that causes a delay and hemoglobin s polymerization by irreversibly binding to the Alpha globe and sub unit of hemoglobin is.
- 00:53:27causing an Alistair a confirmation will change and an increase in auction affinity in vitro the drug was shown to reduce red cell signaling and blood viscosity and improve red cell to form ability, after a favorable phase one to trial investigators conducted a phase three study.
- 00:53:44The hope trial was an international multicenter randomized placebo controlled double blind child a box delatour conducted in six centers across 12 countries.
- 00:53:53They included patients with sickle cell disease have any genotype patients were ages 12 to 65 and had a baseline hemoglobin a 5.5 to 10.5 with one to 10 days inclusive crises per year.
- 00:54:06274 patients were enrolled and we're randomized in a one to one to one fashion to either 1500 milligrams of box delatour 900 milligrams of bugs zilla tour or placebo taken daily.
- 00:54:18Stable doses of hydroxyurea were allowed the trial excluded patients on chronic red cell transfusion therapy.
- 00:54:25Those who had had a transfusion in the past 60 days and anyone who had been hospitalized for crisis within the prior 14 days.
- 00:54:32The primary endpoint was a change in hemoglobin of greater than one gram per deciliter at 24 weeks.
- 00:54:38Secondary endpoints included changing hemoglobin level and laboratory markers for mile assists as well as the annual rate of basic use of crisis.
- 00:54:46This primary endpoint was chosen due to the known mechanism of action of XL a tour, as well as the Association of lower hemoglobin levels, with negative clinical outcomes and sickle cell disease, including stroke pulmonary hypertension and the property.
- 00:55:02Three groups were fairly well matched in terms of age, race or ethnicity and geographic area.
- 00:55:07Most had a severe phenotype either SS disease or sickle beta zero fallacy MIA which you would expect, given the hemoglobin requirement for the study entry baseline hemoglobin was in the eighth and all groups and about two thirds RON baseline hydroxyurea.
- 00:55:23In terms of the primary outcome in the intention to treat analysis 51% of participants on the 1500 milligram dose of fox delatour.
- 00:55:31Had a hemoglobin responsive greater than one gram per deciliter at 24 weeks as compared to 7% with placebo, which was statistically significant.
- 00:55:39The rate was 33% on the 900 milligram dose but this did not reach significance, the percentage of participants who had a hemoglobin response was higher in the 1500 milligram buck sell it to a group than placebo, regardless of concurrent hydroxyurea use or anemia severity at baseline.
- 00:55:58The adjusted mean change in hemoglobin level from baseline to week 24 was 1.1 gram per deciliter in the 1500 milligram group.
- 00:56:050.6 grams per deciliter in the 900 milligram group and negative 0.1 gram per deciliter in the placebo group.

- 00:56:13The P value of less than 0.001 is for the comparison between the 1500 milligram box ella tour group and the placebo group at week 24 note the change in human love and occurred quickly by week two and persisted over time.
- 00:56:28In addition to the significant change in hemoglobin level, there were significant decreases in indirect billy ribbon and percent retweet count.
- 00:56:35Seeing with the 1500 milligram dose as compared to placebo, with a trend toward improvement and absolute ridiculous account and ld ah.
- 00:56:42The percentage of patients undergoing transfusion was similar in all three groups most transfusions were due to acute VOC the annualized rate of the oC was not statistically different that there was a trend toward reduced rate a VOC over time with box delatour.
- 00:57:00adverse events not related to sickle cell disease that occurred or worse in during the treatment period or very common in all three groups.
- 00:57:07Most common as occurring at a rate of 20% or more or headache and diarrhea other as included abdominal pain nausea fatigue brash and pyrex yeah.
- 00:57:17Most of a Grade one or two, and there were no significant differences seen among the three groups in terms of grade three or higher serious at ease or treatment discontinuation due to as.
- 00:57:27Most were judged not to be related to study drug for desecrate on study, none of which were felt to be related to buck sell it or or placebo.
- 00:57:37Based on the anemia benefits seen in the hope trial fox delatour or ox brighter was FDA approved in November 2019 for patients with sickle cell disease ages 12 and older and approval is now extended to include for an older.
- 00:57:51longer term follow up on the impact of UK celador on the occurrence of pain crises is a weighted a five year open label fee three extension study is currently underway.
- 00:58:00And interim analysis of this extension study has shown durable responses in terms of in terms of improved hemoglobin.
- 00:58:06and reduced to model assists and there are no new safety signals for the follow up is needed to determine whether the drug positively impacts any of the longer term complications of sickle cell disease related to anemia and homelessness.
- 00:58:20box ella tour comes as a 500 milligram tablet and the standard dose is 1500 milligrams daily with or without food for adults.
- 00:58:27Those reduction is required for severe liver disease, it may be taken, whether without hydroxyurea and, notably, it may interfere with measurement of hemoglobin subtypes by H plc.
- 00:58:40here's a table for your reference comparing the for FDA approved disease modifying therapies and sickle cell disease.
- 00:58:46These agents, have not been directly compared to each other or two hydroxyurea and they have different burdens of administration monitoring needs adverse event profiles and costs.
- 00:58:58Your patient initiate therapy with excel a tour, in addition to continuing hydroxyurea and Christian was a map.
- 00:59:04or anemia improves, but she continues to have intermittent episodes of severe pain requiring narcotics, she is understandably frustrated and wants to know how she can get rid of this disease, once and for all.

- 00:59:18correction of sickle cell disease at the molecular level can be achieved by completely replacing the patient's bone marrow.
- 00:59:24With bone marrow that contains stem cells, with the correct beta globe and gene from an unexpected tissue match donor most often a sibling.
- 00:59:31The first allergenic transplant for sickle cell disease was reported in 1984 and a pediatric patient with sickle cell disease, who also develop acute leukemia.
- 00:59:40She received a transplant from her brother and was ultimately cured of both diseases.
- 00:59:45Since then, more than 1000 individuals with sickle cell disease have underground transplant predominantly using Hla identical sibling doors.
- 00:59:53Given time constraints, I do not have time for a comprehensive review of transplantation for sickle cell disease, but I wanted to highlight two of the largest reports of outcomes of transportation and sickle cell disease.
- 01:00:05Included in this study or 1000 recipients of Hla identical sibling transplants performed between 1986 and 2013.
- 01:00:13The median age at transplantation was nine years and the median follow up was longer than five years 87% of transplants for my little ablative and the remainder received reduced intensity conditioning.
- 01:00:2484% of patients receive bone marrow as their stem cell source, rather than peripheral blood or cord blood.
- 01:00:30On the left, we see the incidence of chronic graft versus graft versus host disease, over time, according to age, demonstrating a higher rate of chronic gvhd and adults as compared to children.
- 01:00:42On the right we have overall survival according to stem cell source in the entire group the five year overall survival rate was excellent at 92.9%.
- 01:00:51However, age, had a significant impact on survival rates, the five year overall survival rate was 95% for those less than 16 years of age, but fell to 81% for those aged 16 years and older.
- 01:01:06In this second study investigators analyze data from over 900 transplants in patients with sickle cell disease between 2008 and 2017.
- 01:01:14With patients grouped according to donor type and conditioning regimen recipients of Hla match sibling transplant are shown in blue.
- 01:01:22When the donor was a match sibling overall survival was excellent at 96% with an event free survival of 89% across all age groups, three years after transplantation.
- 01:01:33Unfortunately, with rare exceptions all reported outcomes, including overall survival event free survival and graft failure from donors, other than a chilly match siblings were significantly worse than those from a match sibling donor.
- 01:01:45There was also a much higher incidence of acute and chronic graft versus host disease with each other donor types.
- 01:01:54As these two studies and others have demonstrated stem cell transplantation can be cured and sickle cell disease.
- 01:01:59With excellent survival rates, particularly in younger patients with a match sibling donor but there remains significant limitations with transplant for sickle cell disease that must be addressed.

- 01:02:08First there is the issue of donor availability fewer than 20% of patients with sickle cell disease in the United States have a match sibling donor and as similar percentage have a matched unrelated donor in the registry.
- 01:02:20use alternative donor types, including unrelated donors unrelated cord blood and happily identical related donors have improved access to transplant and recent studies have shown some success using these other donor types.
- 01:02:33toxicity is also a significant concern, particularly in adults who have chronic organ dysfunction in these cases non ablative or reduced intensity conditioning regimens may be considered.
- 01:02:46The risks of gvhd increase with age and new medications to prevent and or treat graft versus host disease may reduce this risk.
- 01:02:54There are concerns related to infertility, as well as the rest of secondary malignancies due to Milo ablative conditioning.
- 01:03:01And finally, determine determining which patients are most appropriate for transplant can be a challenge.
- 01:03:07Last year, the American society of hematology published guidelines regarding transplantation for sickle cell disease.
- 01:03:13These guidelines help address which individuals with sickle cell disease should be considered for transplant based on specific sickle cell disease complications and age.
- 01:03:22They also provide guidance on the type of transplantation in terms of conditioning regimen type of donor and stem cell source.
- 01:03:29In general transplant may be considered for those patients who have more severe disease manifestations, such as stroke life threatening acute chest syndrome progressive heart lung or kidney disease or life limiting pain.
- 01:03:43sickle cell disease has long been an attractive application for a gene therapy approach, given that the phenotype is the result of a single point mutation in the beta global gene.
- 01:03:54Because gene therapy is autologous it avoids the inherent risks of graph rejection and graft versus host disease that accompany allergen a transplant and extends the possibility of a cure to all patients.
- 01:04:06A comprehensive review of gene therapy is beyond the scope of this talk, but I wanted to give you a brief overview of the general concepts and targets of gene therapy and sickle cell disease.
- 01:04:16Unlike gene therapy for hemophilia which typically uses a direct injection IE liver directed of a viral vector.
- 01:04:23The approach for sickle cell disease first requires gene modification ex vivo of the patients out of wedlock stem cells.
- 01:04:31There are four basic ways the gene therapy is performed in sickle cell disease teen addition gene editing gene silencing and finally gene correction.
- 01:04:42Although gene correction is currently the least efficient method efforts are underway to improve gene production techniques, this is the only type of gene therapy that currently aims to eliminate hemoglobin as production and introduce a non suckling hemoglobin simultaneously.

- 01:04:59Most trials of gene therapy and sickle cell disease have involved ex vivo techniques, common to all approaches, is the use of autologous CD 34 positive medical webex stem and presented ourselves.
- 01:05:11These cells are collected by a free service after mobilization into the peripheral circulation from the bone marrow.
- 01:05:17Unlike mobilization and malignancies here we typically use a drug called lyrics for a cx er for antagonist rather than G CSF.
- 01:05:26As G CSF is contraindicated and sickle cell disease, because it can trigger crises and other adverse events.
- 01:05:32Most gene therapy protocols have implemented red blood cell exchange transfusions as a pre transplant preoperative regimen to prevent the occurrence.
- 01:05:40Of sickle cell disease related morbidity associated with the stem cell mobilization and a free says procedure.
- 01:05:46The harvest itself then genetically modified so that they either produce more fetal hemoglobin or express a fetal like hemoglobin encoded by a modified beta globe and gene.
- 01:05:57The patient that undergoes conditioning typically with Milo ablative chemotherapy to make room for the autologous transplant the modified cells are then re-infused, and this is followed by a graph replication production of hemoglobin and hopefully lifelong persistence.
- 01:06:15These diagrams describe the three most common approaches to gene therapy and sickle cell disease at this time.
- 01:06:21In all three approaches autologous stem cells are collected by a freezes the cells are then genetically engineered by one of three methods.
- 01:06:29And the top example a modified fetal like beta globe and gene is added through 10 deduction valenti viral vector this produces a fetal like non sickly and hemoglobin called HPA ti 87 Q.
- 01:06:42In our results from the phase one to study using this approach we're just published two weeks ago in the New England journal.
- 01:06:48Among the 25 patients who could be evaluated at six months, so if you're a stickler related business news and events had stopped hemoglobin levels had increased to more than 11 grams per deciliter and the non-suckling hemoglobin was detected and 40% of total keep of look at.
- 01:07:04The bottom two approaches involve the suppression of the expression of bcl 11 a by targeted genetic modification bcl 11 a is a transcription factor, the represses the synthesis of gamma globe and and therefore reduces production of fetal hemoglobin and red cells.
- 01:07:22The Middle diagram describes a gene editing approach this approach uses a rainbow nuclear protein consisting of cast nine nucleus, and a guide RNA the targets, a small enhancer segment of the.
- 01:07:35A small edit is made in the enhancer hindering its ability to drive bcl have been a production this then allows the synthesis of gamma globe and therefore hemoglobin F and red cells.
- 01:07:46In the bottom diagram there is knocked down a B cell 11 a messenger RNA using an inhibitory micro RNA unquote encoded violently viral vector.

- 01:07:55This leads to an increase in gamma globe and therefore hemoglobin F production there are ongoing studies, using all of these approaches and sickle cell disease and none are yet currently FDA approved.
- 01:08:08Despite the promise of a cure questions and concerns remain regarding gene therapy and sickle cell disease.
- 01:08:13What about long term results will induction have high levels of anti-cyclone hemoglobin prevent all disease complications and justify the rigorous and expensive this procedure.
- 01:08:23will be in graph might be durable what, if any, chronic disease complications can be reversed.
- 01:08:29There are safety concerns with all current therapies that involve genetic manipulation which include vector mediated in social media genesis and off target gene editing.
- 01:08:39There are also concerns about risks inherent to the high dose chemotherapy required for autologous bone marrow transplantation.
- 01:08:45Last year or two cases of xml MDS developed after lengthy globe and gene therapy the definite cause of these events is uncertain, but they may be related to the use of you sell fan, and the conditioning regimen and searchable mutagenesis both or neither.
- 01:09:00cost is also a significant concern experts believe that gene therapy products for sickle cell disease will probably cost around $1 million for a one-time dose.
- 01:09:10Approximately 100,000 people in the United States have sickle cell disease and half are enrolled and Medicaid programs.
- 01:09:16innovated payment of innovative payment models are therefore urgently needed to ensure equitable access to these therapies.
- 01:09:24Current gene therapy techniques require a robust hospital infrastructure, which is not available in many parts of the world or sickle cell disease is most prevalent.
- 01:09:33Does these therapies are unlikely to be available to the majority of patients with sickle cell disease.
- 01:09:39In vivo gene therapy could be conducted on a large scale, as it does not require an autologous transplant, there are currently collaborations trying to develop such a therapy to expand access to these treatments on a global scale.
- 01:09:51The NIH cure sickle cell initiative was established in.
- 01:09:55To address these issues and to accelerate the development of these curative therapies for patients with sickle cell disease.
- 01:10:03So, in summary, over the last several years advances in our understanding of the pathophysiology of sickle cell disease has led to the development of several targeted therapies.
- 01:10:12We now have four FDA approved agents addressing hemoglobin polymerization faisal occlusion endothelial dysfunction and inflammation.
- 01:10:21The optimal sequence or combination of therapies that maximizes benefits and minimize the side effects is unknown, we need to use shared decision making to personalize selection of therapy.
- 01:10:32Given the long term data I recommend hydroxyurea for all symptomatic patients.

- 01:10:36Just paint episodes continue despite hydroxyurea or if hydroxyurea is not tolerated I would consider adding prison was a map and or l glutamine and if a patient is symptomatic anemia I consider adding buck celador.
- 01:10:49curative approaches are possible, but there are limitations transplantation for match sibling donors are very effective, particularly in younger patients.
- 01:10:57The use of alternative donors less intensive conditioning regimens and more effective gvhd prophylaxis hope to extend transplant as an option to more patients.
- 01:11:07And finally gene therapy is an exciting potential option, for there are multiple challenges that must be overcome before gene therapy becomes widely accepted available for all patients with sickle cell disease.

Unknown Speaker

01:11:18Thank you.

Izzy Budnick

01:11:28Great thanks so much Dr Davidson.

- 01:11:31we've got some questions coming into the chat.
- 01:11:34The first one is so firstly thanks for the great talk is there an effort to compare newer medications for sickle cell to hydroxyurea for superiority, or at least non-inferiority.

Kelly Davidson

01:11:48So I am not aware of any trials comparing them, I think you know many of these newer studies did include patients who are already taking hydroxyurea and since.

- 01:11:58These drugs have different mechanisms of action, I think the idea is to try to figure out how we can combine them to best you know, improve outcomes in patients with sickle cell disease so I'm not aware of any trials comparing the drugs head to head.

Izzy Budnick

01:12:13The question I have is um what, what are the efforts to sort of help boost enrollment into this clinical trials for sickle cell disease it's.

- 01:12:23it's notable that you know, for instance, I can dari only had a sample size of 230 patients for such a common condition is that something you've experienced kind of these barriers for enrollment.

Kelly Davidson

01:12:35yeah I mean we have struggled to enroll patients that only study we've had open recently was a transplant trial, and we really struggled to get patients.

- 01:12:44to even consider that trial, you know I don't know any specific interventions that were done in those studies to try to improve enrollment but certainly that is an issue trying to get people to participate me studies.

Izzy Budnick

01:13:00Another question is, how do you kind of view the.

- 01:13:05How do you view the like the added benefits of books, all the tour probably not pronouncing that correctly.
- 01:13:10When you know that the primary outcome was just an increase in you know one point on human blood in your experience for patients who have symptomatic anemia to some end up having a pretty significant improvement and thus their symptoms also improve or what's been your experience.

Kelly Davidson

01:13:27So you know what I think the benefit of buck Salvatore is you know any improvement in hemoglobin and the possibility that they will require fewer transfusions is beneficial, I mean.

- 01:13:38We really try to avoid transfusions and our patients with sickle cell disease, because of the risk of iron overload. And aloe immunization and we do have patients, like the case, I presented this is actually a real patient.
- 01:13:49who have history of significant key melodic transfusion reactions and we really have.
- 01:13:55Problems transfusing them and try to avoid that at all costs, so you know, even though a grand doesn't seem like a lot if that does reduce transfusions you know that is something that I think is a benefit to patients.

Izzy Budnick

01:14:09um could you comment on sickle cell disease treatment in African countries and outcome.

Kelly Davidson

01:14:16yeah so that's a really great question um when we've been at ash I've been impressed, there have been several studies coming out of Nigeria.

- 01:14:24A lot of them looking at hydroxyurea because they just really lack the infrastructure to do some of these sort of newer agents, but the hydroxyurea studies in the African countries have been similarly positive to the MSA trial.
- 01:14:39And you know I think that's really what the target is is getting more patients to take hydroxyurea and some of these basic things like immunizations and prophylactic antibiotics.
- 01:14:51But yeah I mean it's there's a huge number of patients in these African countries suffering with sickle cell disease.

Izzy Budnick

01:14:59awesome and then.

- 01:15:03Who will round out with two more questions, one is from Dr Wolf, how did they set the price point of a million dollars for gene therapy.

Kelly Davidson

01:15:13I don't know the answer that I think that's just what I've read you know that they expect that will be the cost, but I don't I don't know how they came up with that.

Izzy Budnick

01:15:22And then, and then the last one there's no less no way I can pronounce this correctly off the fly, but any experience with oren entre. The guards and docs oh boy.

Kelly Davidson

01:15:35I do not have any experience with.

Unknown Speaker

01:15:36Okay.

Izzy Budnick

01:15:39I apologize for not even know what that is but.

- 01:15:42Anyway, anyone else has any questions pop them in the chat if not it's one o'clock and really appreciate the update on cell disease thanks so much.

Kelly Davidson

01:15:53Thank you.