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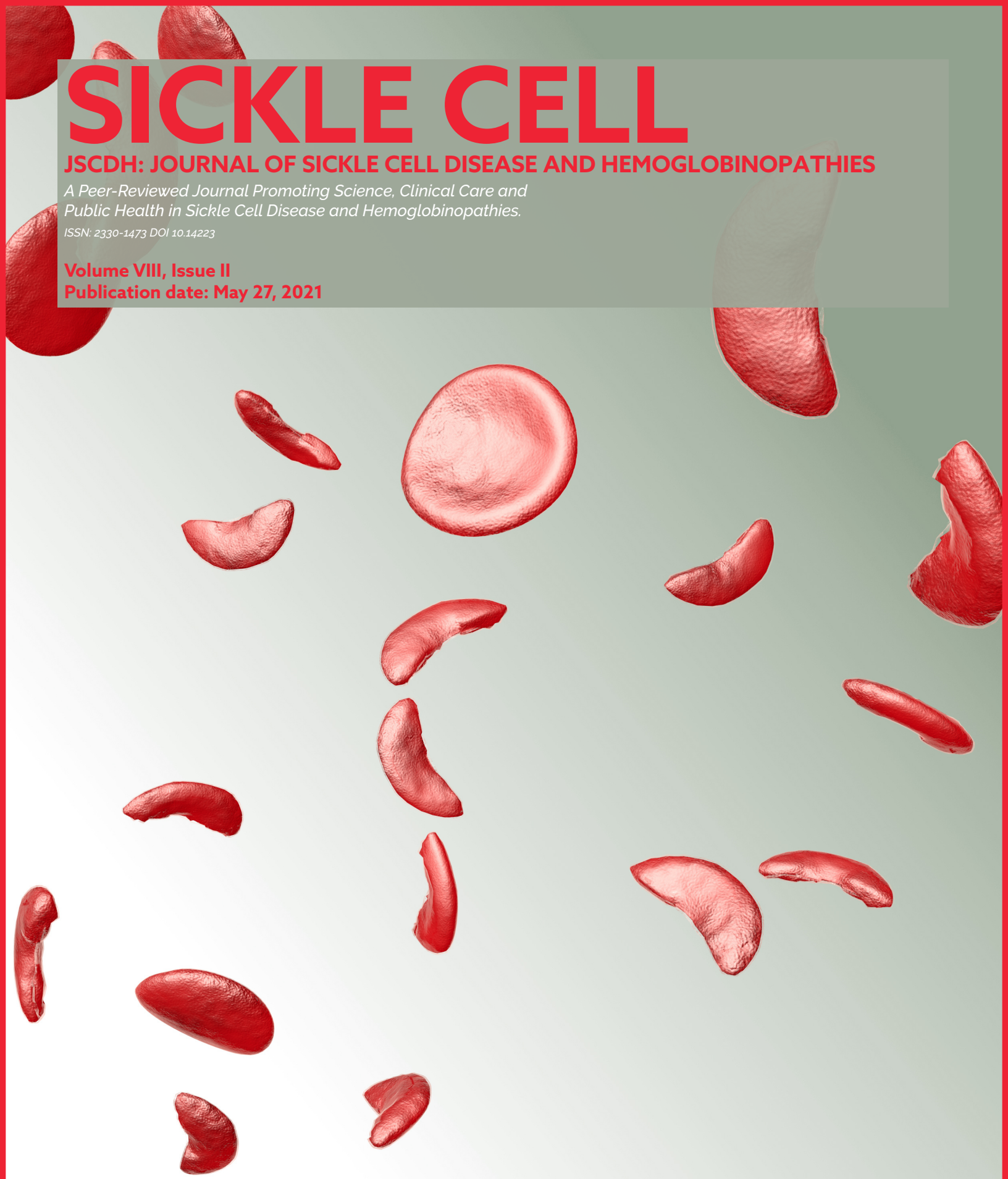

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TOP ABSTRACTS
ORAL PRESENTATIONS
Presenting: Saturday, May 29, 2021 at 3:45 PM

JSCDH-D-21-1038905

INHIBITION OF MONOACYLGLYCEROL LIPASE REDUCES CHRONIC NOCICEPTION IN BERKELEY SICKLE MICE

Authors: Kennedy N. Goldsborough, BSc[2], Rebecca Moncayo, BSc[2], Karan Muchhala, PhD[2], M Imad Damaj, PhD[2], Kalpna Gupta, PhD[1], Wally R. Smith, MD[2], Joyce Lloyd, PhD[2], Hamid Akbarali, PhD[2], Aron Lichtman, PhD[2]

Affiliation: *[1]University of California - Irvine, [2]Virginia Commonwealth University*

Background: Chronic pain is a major problem among adults with Sickle Cell Disease (SCD) and contributes to significant functional disability. Although opioids remain the standard of care to treat SCD chronic pain, their myriad adverse effects (e.g., constipation, respiratory depression, abuse liability, dependence, tolerance) limit their therapeutic utility. Thus, a pressing need exists to identify effective non-opioid analgesic strategies to reduce SCD chronic pain and improve motor function. The endocannabinoid system contains several non-opioid targets that may potentially treat pain related to SCD. In particular, inhibitors of the major degradative enzyme of 2-arachidonoylglycerol, monoacylglycerol lipase (MAGL), reduce nociceptive behavior in neuropathic and inflammatory preclinical models of pain through cannabinoid receptor-dependent and -independent mechanisms; however, these drugs have yet to be tested in models of SCD. Berkeley SCD mice (HbSS-BERK) express human sickle hemoglobin, HbS, and display a similar phenotype as SCD patients, thus representing a useful tool to evaluate disease pathophysiology and investigate novel therapeutic strategies. HbSS-BERK mice exhibit mechanical and thermal hypersensitivity, as well as diminished grip strength compared to HbAA-BERK (humanized control) mice. Here we test the following hypothesis: MAGL inhibition will ameliorate chronic nociceptive behaviors in HbSS-BERK mice.

Methods: Male and female (6-8 months of age) HbSS-BERK and HbAA-BERK (control) mice were used as subjects for these experiments. Stimulus-evoked behaviors were assessed using the Von Frey and Hot Plate tests, while motor functional behaviors were assessed using the Grip Strength and Inverted Screen tests. The selective MAGL inhibitor MJN-110 (5 mg/kg, i.p.) was given one hour prior to testing. Data were analyzed using one- or two-way Analysis of Variance (ANOVA) and Tukey or Sidak post-hoc analysis when appropriate.

Results: HbSS-BERK mice displayed profound mechanical allodynia and thermal hyperalgesia, as well as diminished grip strength and poor performance in Inverted Screen compared to control mice. Sex differences were not observed in any of the tests. Moreover, DRG neurons (L4-L6) isolated from HbSS-BERK mice exhibit hyperexcitability. MJN-110 (5 mg/kg) significantly reduced mechanical allodynia and thermal hyperalgesia at 1 and 2 hours post-injection, and improved inverted screen performance 1 hour post-injection. Importantly, HbSS-BERK mice given seven days of daily injections of MJN-110 (5 mg/kg) displayed sustained antinociception that did not undergo tolerance.

Conclusion: These initial findings validate that HbSS-BERK mice display severely hyperalgesic phenotype that is accompanied by functional behavioral deficits (including reduced grip strength and impaired performance in the Inverted Screen test). The identification and characterization of motor functional deficits in these SCD mice, as well as the subsequent evaluation of pharmacological targets in these same assays may improve the translatability of our findings to the human condition. Ongoing studies are examining the effects of MJN-110 on motor functional deficits. These emerging data suggest that MAGL inhibition represents a viable strategy to reduce chronic nociceptive behaviors in the HbSS-BERK mouse model.

JSCDH-D-21-1039952

HEME MEDIATED ENDOTHELIAL CELL ACTIVATION AND DAMAGE IS PREVENTED BY HEMOPEXIN IN VITRO

Authors: Jacqueline Adam, Lisa Ventrici, Valérie Verdon, Thomas Gentinetta, Svetlana Diditchenko, Alexander Schaub, Gregory Kato, Nathan Brinkman, Adrian Zuercher

Affiliation: *CSL Behring AG, Research and Development, Bern, Switzerland*

Background: Hemoglobin (Hb) is one of the most abundant proteins in the human body. Upon rupture of red blood cells, cell-free Hb may initiate adverse pathophysiological reactions. A well characterized example of Hb-triggered pathophysiological disorders is sickle cell disease (SCD), characterized by the expression of abnormal hemoglobin-S (HbS) instead of the normal HbA due to a single nucleotide mutation in the β-globin gene. Polymerization of HbS shortens the lifespan of sickle red blood cells and promotes intra- and extravascular hemolysis. In cell-free Hb ferrous Hb (Fe2+) is oxidized into ferric Hb (Fe3+) promoting the dissociation and transfer of heme into lipid compartments where the generation of cytotoxic and pro-inflammatory reaction products are triggered. These processes eventually lead to endothelial cell activation and damage. The natural plasma protein hemopexin is a heme scavenger and binds heme in a 1:1 binding ratio with highest affinity of all known proteins. Hemopexin-bound heme is rendered relatively non-reactive and is delivered safely to hepatocytes for endocytosis and degradation. Here we show the protective function of hemopexin on endothelial cells exposed to elevated levels of cell-free heme.

Methods: Human umbilical vein endothelial cells (HUVEC) were exposed in vitro to heme in the presence or absence of different hemopexin doses. As a read-out, different markers for endothelial cell activation were analyzed by Western Blot, multiplexed particle-based flow cytometry (Luminex), flow cytometry or on mRNA levels by qRT-PCR.

Briefly, confluent HUVEC were preincubated with hemopexin at different concentrations for 5 min before stimulation with heme for various lengths of time. Following stimulation cells were analyzed by Western Blot for the expression of HO-1, a sensitive marker for heme exposure. Expression of pro-inflammatory cytokines IL-6 and IL-8, cell adhesion molecule VCAM-1 and blood glycoprotein von Willebrand factor (vWF) were analyzed on mRNA levels by qRT-PCR or in cell culture supernatants by Luminex. All these investigated proteins are well known markers for endothelial cell activation.

Alternatively, heme stimulation of hemopexin-preincubated HUVEC was conducted for 25 min and cells were analyzed by flow cytometry for membrane bound P-Selectin expression, another robust endothelial cell activation marker.

Results: In the absence of hemopexin, heme consistently showed strong stimulatory capacity on HUVEC reflected in a robust upregulation of pro-inflammatory cytokines, VCAM-1, vWF, HO-1 and P-Selectin. Increasing hemopexin concentrations during heme-mediated stimulation led to a dose-dependent reduction in HUVEC activation markers and once an equimolar ratio between heme and hemopexin had been reached, the expression of HO-1, P-Selectin, VCAM-1, vWF and pro-inflammatory cytokines was lowered to background levels.

Conclusion: The presented data underlines on the one hand the stimulatory capacity of heme on endothelial cells and demonstrates on the other hand the efficient heme scavenging potential of hemopexin. Hemopexin-bound heme molecules are rendered non-reactive and consequently, hemopexin potently prevents the pro-inflammatory effect of heme on endothelial cells. This effect results in a strongly reduced expression of endothelial activation markers in heme-stimulated cells under an equimolar ratio of heme and hemopexin. Hence, our study

suggests a protective role of hemopexin for endothelial cells exposed to elevated levels of cell-free heme due to intravascular hemolysis, a phenomenon seen in Hb-triggered pathophysiological disorders such as SCD.

JSCDH-D-21-1038106

VENOUS THROMBOEMBOLISM ASSOCIATED WITH INCREASED SICKLE CELL DISEASE SEVERITY & MORTALITY

Authors: Julia T. Newman[1], MD, Sarah Khan, MD[1], Romy Lawrence, MD[2], Vishal Gupta, MD[3], Mark Sloan, MD[4], Robyn Cohen, MD[4], Seyed Mehdi Nouraie, MD PhD[5], Elizabeth S. Klings, MD[4]

Affiliation: *[1]Boston Medical Center, [2]Northwestern University, [3]Beth Israel Deaconess Medical Center, [4]University of Boston School of Medicine, [5]Department of Medicine University of Pittsburgh*

Background: By age 40, 11-12% of patients with sickle cell disease (SCD) experience a venous thromboembolism (VTE). VTE is associated with a high recurrence rate and a nearly three-fold increased mortality risk. We hypothesized that patients with SCD and VTE have increased disease severity characterized by increased vasoocclusive events (VOE), cardiopulmonary dysfunction and mortality.

Methods: We performed a retrospective chart review of 402 patients with SCD who received care at Boston Medical Center/Boston University between 2003 and 2019. VTE was defined as deep venous thrombosis (DVT) diagnosed by Duplex ultrasound and/or pulmonary embolism (PE) diagnosed by ventilation-perfusion scanning or computed tomography angiography. We recorded Emergency Department visits, hospitalizations, VOE and acute chest syndrome (ACS) episodes, laboratory and echocardiography data, and medication use. For VTE patients, clinical data 1- and 5- years post-VTE were compared to 1-year pre-VTE. For non-VTE patients, data were obtained at baseline and five years later. Rates of VOE, ACS, Emergency Department (ED) visits and hospitalizations before and after VTE were compared to those without VTE. Data were analyzed using Stata 14.2

Results: Of 402 individuals with SCD, 251 (62%) were HbSS/HbSβ0 and 227 (56%) were female. A VTE occurred in 75 (19%); thirty-five (46%) had a DVT, 50 (66%) had a PE, and 9 (8%) had both. Thirty-six (50%) did not have a provoking event other than SCD. VTE patients had a higher frequency of prior ACS ($p<0.001$), stroke ($p=0.008$), surgical splenectomy ($p=0.005$), and avascular necrosis ($p<0.001$) than those without a VTE. The yearly rate of ED visits (median of 21.0 vs. 4.0, $P = 0.004$) and hospital admissions (12.0 vs. 2.0 admissions, $P<0.001$) was higher for patients with VTE versus those without VTE. Interestingly, those with a VTE did not have an increased frequency of elevated pulmonary pressures or right-sided dysfunction by echocardiography compared with those without a VTE. Mortality was increased in those with a history of VTE; observed in 10 of 75 (13%) VTE patients compared to 19 of 327 (6%) non-VTE patients ($p=0.04$).

Conclusion: Patients with SCD and a VTE had higher rates of SCD related complications, increased hospital utilization and mortality compared to those who did not have VTE. Interestingly, this mortality risk was not associated with echocardiographic evidence of pulmonary hypertension. These findings need to be confirmed in a larger prospective study.

ABSTRACT BREAKOUT SESSION I
CLINICAL RESEARCH ORAL PRESENTATIONS

Presenting: Sunday, May 30, 2021 at 10:30 AM

JSCDH-D-21-1035412

COGNITION AND EDUCATION BENEFITS OF INCREASED HEMOGLOBIN AND BLOOD OXYGENATION IN CHILDREN

Authors: Joanna P. MacEwan, PhD[1], Allison King, M.D., M.P.H., Ph.D. [2], Andy Nguyen, PhD[3], Anuj Mubayi, PhD[1], Irene Agodoa, MD[3], Kim Smith-Whitely, MD[4]

Affiliation: *[1]PRECISIONheor, [2]Washington University School of Medicine, [3]Global Blood Therapeutics, [4]Children's Hospital of Philadelphia*

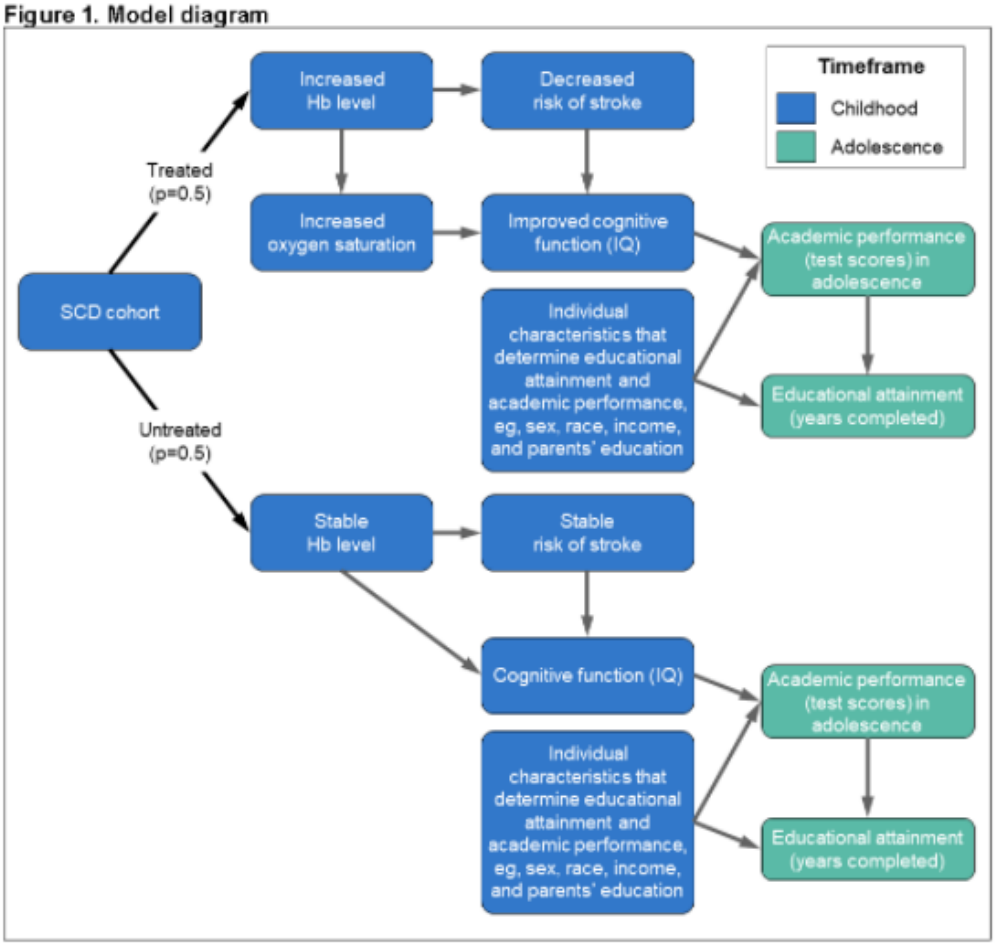
Background: Chronic anemia in individuals with sickle cell disease (SCD) has been associated with impaired intellectual functioning and lower academic achievement. Among these individuals, decreased hemoglobin (Hb) is associated with increased risk of stroke and lower oxygen saturation (SpO2), which are both associated with lower intelligence quotient (IQ) scores. Thus, increasing Hb and SpO2 in individuals with SCD may increase IQ and educational attainment.

Methods: A cohort simulation model was built to reflect the pediatric SCD population and used to estimate how improvements in pediatric cognitive function, as measured by IQ, generated from randomized treatment for SCD, affect academic performance and educational attainment. Model parameters were identified in the literature. The model contained two key stages: childhood (preschool and school age, < 10 years) and adolescence (≥10 years). The model framework is shown in Figure 1. In the first stage, children in the treated group had a mean Hb increase of 1.1 g/dL and increased SpO2, which impacted IQ by directly increasing it and preventing deterioration of IQ over time. Hb increase also decreased the risk of stroke. In the second stage, adolescence, IQ was a determinant of academic performance as measured by the Armed Forces Qualification Test scores. These scores and other individual characteristics (including noncognitive skills) were employed to model years of education completed. Key model parameters are summarized in Table 1.

Results: In the simulated cohort of 2000 children and adolescents with SCD (52.5% female, 50% treated, 50% untreated), the incidence of stroke was 38.8% lower among the treated group compared with the untreated group. 4.1% of those in the treated group experienced a stroke versus 6.7% of those in the untreated group. The average IQ among those treated was 91.1, compared with 83.0 in the untreated group—a difference of 9.7% (Figure 2A). Finally, high school completion rates (≥12 years of education completed) were 80.3% higher among the treated group; 78.6% of the treated group completed ≥12 years of education compared with 43.6% in the untreated group (Figure 2B).

Conclusion: As demonstrated in this analysis, children with SCD with increased Hb and SpO2 have better cognitive function (IQ) and lower risk of stroke. Our model predicts that an average 1.1 g/dL improvement in Hb may be associated with improved neurocognition and educational outcomes. These improvements may also generate benefits not captured by our model, including improved quality of life, employment, and income among individuals with SCD.

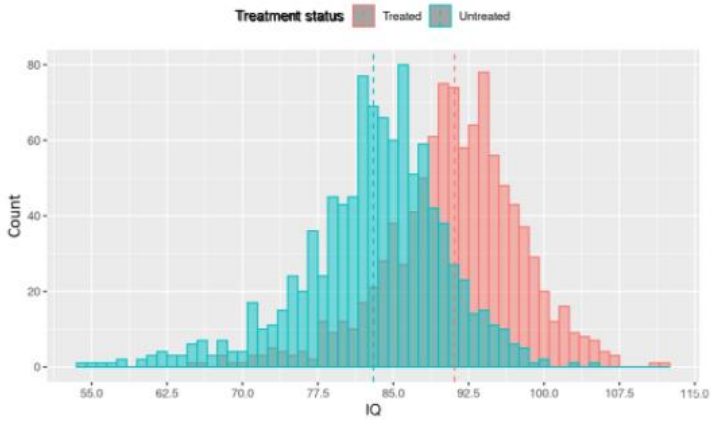
Figure 1. Model diagram



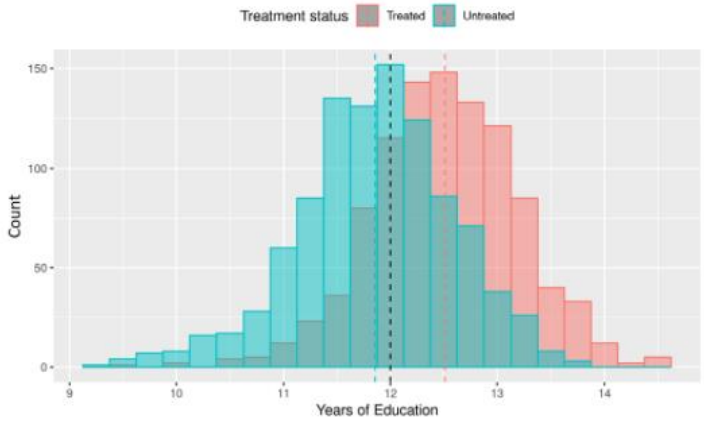
Hb, hemoglobin; IQ, intelligence quotient; SCD, sickle cell disease.

Figure 2. Distribution of IQ score (A) and years of education completed (B) by treatment status

(A)



(B)



IQ, intelligence quotient.

Table 1. Key model parameter values

Parameter	Value	Sources
Treatment effect on hemoglobin	1.1 g/dL increase (95% CI: 0.9-1.4)	Vichinsky et al. (2019)
Treatment effect on oxygen saturation	3.1 percentage point increase per 1 g/dL increase in Hb	Blyden et al. (2018)
Relative stroke risk (infarctive)	1.85 (95% CI: 1.32-2.59) per 1 g/dL decrease in Hb	Ohene-Frempong et al. (1998)
Reduction in IQ score in stage 1 resulting from stroke	–15.86	Kawadler et al. (2014)
Reduction in IQ score in untreated state between stages 1 and 2 independent of stroke/infarct status	–5	Steen et al. (2005), Wang et al. (2001), King et al. (2014)
Baseline initial IQ	Mean 89.18 (95% CI: 86.36-92.00)	Kawadler et al. (2014)
Baseline initial stroke risk	Mean 7.2% (SD 0.7)	DeBaun et al. (2014)

IQ, intelligence quotient.

COMPARING HOSPITALIZED SICKLE CELL DISEASE PATIENTS WITH AND WITHOUT SARS COV-2 INFECTION

Authors: Rich Kodama[1], Ayanna Baptiste, MD[1], Angelica Singh, MD[1], Marshall Glesby, MD[2], Harold Horowitz, MD[2]

Affiliation: *[1]NewYork-Presbyterian Brooklyn Methodist Hospital, [2]Weill Cornell Medicine and NewYork Presbyterian Hospital*

Background: COVID-19 has had significant impact on the health of individuals worldwide including those with Sickle Cell Disease (SCD). SCD has been variably reported to be a risk factor for severe disease from COVID-19 and is considered a high-risk group for the development of severe COVID-19 disease (1-3). To date, there have been no comparison studies of hospitalized patients with SCD diagnosed with COVID-19 compared to those without COVID-19.

Objective:

- To evaluate disease severity between groups comparing rates of complications such as acute chest syndrome (ACS), intensive care unit (ICU) admissions, and mortality.
- To compare clinical and laboratory findings of patients admitted with SCD and COVID-19 to SCD patients without COVID-19 to determine whether there are ways to differentiate the two presentations.

Methods: This is a single institution retrospective review of laboratory confirmed Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) patients with SCD compared to those without infections admitted to NewYork-Presbyterian Brooklyn Methodist Hospital between March 1, 2020 and May 31, 2020. Patient clinical characteristics were manually extracted from electronic medical records. ACS was defined by respiratory symptoms accompanied by fever and CXR findings during admission. Continuous variables are expressed as medians (Q1, Q3) and compared using the Wilcoxon rank-sum test. Categorical variables were compared using Fisher's exact test. P-value < 0.05 considered significant. Institutional Review Board approval was obtained.

Twenty-three SCD patients were admitted; 12 confirmed to have SARS-CoV-2 infection by nasopharyngeal swab. Median age, gender, body mass index, and prior hydroxyurea use were similar between groups (Table 1). Both groups similarly perceived presenting symptoms as "pain crisis" (Table 1). Those with genotype HbSC were more commonly admitted with COVID-19 than without COVID-19 compared to other genotypes (41.7% vs 0%, p = 0.037). None received remdesivir, steroids, tocilizumab, or convalescent plasma.

Patients infected with SARS-CoV-2 had significantly higher rates of ACS (66.7% vs 9.1%, p=0.033), higher admission temperature (37.4oC vs 36.9oC, p=0.005), and higher peak temperature (38.9oC vs 37.3oC, p=0.002) (Table 1). They also had more febrile days (1.5 vs 0, p=0.002), and longer length of stay (LOS) (9.5 vs 3.0, p=0.014). The frequency of oxygen saturation (SpO2) < 94% was more common in the SARS-CoV-2 infected group but not significantly so (Table 1). One SARS-CoV-2 infected SCD patient required a non-rebreather, none were intubated, and none with COVID-19 died.

Documented initial and peak laboratory values were not statistically different (Table 1). However, chest X-ray abnormalities were significantly higher among patients with COVID-19 (Table 1). Rates of ICU admission, vasopressors, acute kidney injury, renal replacement therapy, acute venous thromboembolism, and transfusions were similar between groups (Table 1).

Results: This study demonstrated that hospitalized SCD patients infected with SARS-CoV-2 had

significantly more ACS and were hospitalized longer than SCD patients without such infection i.e. they seemed sicker than those who did not have COVID-19. Although the admitting temperature was higher in the COVID-19 cohort, in both cohorts the majority of patients had normal temperatures making this parameter difficult to differentiate the two groups. Cough was also more frequently reported, but not statistically significantly so in SCD patients with COVID-19. This finding may be due to the small number of patients.

For most laboratory parameters evaluated on admission, the two cohorts could not be readily distinguished. Appreciating the small numbers of patients in both of our cohorts, it is noteworthy that such parameters as C-reactive protein, ferritin, LDH, and D-dimer, which are used to measure the severity of COVID-19 illness, are all frequently elevated in patients with sickle cell crisis (4-7). Ferritin, LDH, and D-dimer were all elevated in many of the non-SARS-CoV-2 infected patients. Perhaps the most often used parameter to define "severe" COVID-19, the oxygen saturation, was < 94% in nearly 86% of patients without SARS-CoV-2 infection and therefore may not be particularly useful to define severe disease in patients with SCD. Differentiating patients with sickle cell crisis with and without COVID-19 may be difficult based upon both clinical presentation and laboratory parameters.

The most significant differentiating factor between the two cohorts was the high frequency (66.7%) of ACS among patients with SCD and COVID-19 compared to those without COVID-19. As Sivalingam and colleagues have noted and we corroborate, ACS may be an indicator of SARS-CoV-2 infection in patients with SCD (8).

We appreciate that SCD is considered a high-risk comorbidity for developing severe COVID-19 (1,9). This is based largely upon data comparing outcomes among black persons infected with SARS-CoV-2 with and without SCD (1). Our outcomes were better although we concur that using current definitions, patients with SCD and COVID-19 presented with severe disease. The difference in outcomes may be due to the fewer number of cases reported here or perhaps that the population in this study is different than that reported by the Medical College of Wisconsin group. The population reported herein had relatively mild disease as demonstrated by the fact that none were admitted to the ICU and the lack of mortality without specific treatment. These data corroborate a French study of 83 patients and a case series of mainly pediatric patients (2, 3). This may be due to the overall young age in the population presenting with SCD crises. It is also of note that the SARS-CoV-2 infected SCD patients reported herein had a median LOS of 9 days which is similar to patients in the remdesivir arm of the Adaptive COVID-19 Treatment Trial (ACTT) comparing remdesivir to placebo (10). In that study the median LOS was 10 days in the treatment arm versus 15 in the placebo arm (10). The patients in our study did not receive treatment with remdesivir or steroids and had a similar LOS to remdesivir treated patients in the ACTT study. While genotype HbSC is generally a less severe form of SCD than HbSS, poor outcomes in HbSC patients with COVID-19 have been observed (1). Although genotype HbSC was more commonly admitted in patients with COVID-19 compared to those without COVID-19, due to the small numbers we did not attempt to compare outcomes which were good in both groups.

This study has several limitations including as noted the small sample size and the facts that it is from a single institution and retrospective. Furthermore, the limited biomarker data in the non-SARS-CoV-2 reduced our power to detect differences between group

Conclusion: In conclusion, patients with SCD and COVID-19 who were hospitalized had disease that by current definitions would be classified as severe COVID-19 disease and had a higher incidence of ACS as well as a more prolonged length of hospitalization than those SCD patients admitted to the hospital without COVID-19. However, due to confounding clinical signs and laboratory abnormalities inherent in SCD patients with sickle cell crisis, the two

populations were difficult to differentiate at presentation. Furthermore, given these confounding factors in SCD patients infected with SARS-CoV-2, the reported incidence of severe COVID-19 may be overestimated in the SCD population.

JSCDH-D-21-1036925

EARLY RESULTS FROM A PHASE 1/2 STUDY OF ARU-1801 GENE THERAPY FOR SICKLE CELL DISEASE

Authors: Christopher Lo, BS, Courtney R. Little, BSN, Joseph W. McIntosh, MD

Affiliation: *Aruvant Sciences*

Background: ARU-1801 is a gene therapy to treat sickle cell disease, containing autologous CD34+ hematopoietic stem cells that are transduced with a lentiviral vector encoding a modified γ-globinG16D gene for expression of HbFG16D. Safety and efficacy is being studied in patients with SCD in the ongoing Phase 1/2 MOMENTUM study (NCT02186418, https://momentumtrials.com/). Due to the end-organ damage and increased cancer risk in patients with SCD, it is important to explore the possibility of using reduced-intensity conditioning to reduce the risks of myeloablative conditioning. As a highly potent anti-sickling globin, HbFG16D is believed to allow ARU-1801 to be effective with reduced intensity conditioning, resulting in shorter hospitalizations and fewer toxicities than myeloablative transplants, making gene therapy more available to a broader group of SCD patients. We present long-term results from the first two patients (P1 and P2) and 10-month follow-up on patient 3 (P3), the first patient treated with a newer manufacturing process used to improve engraftment and increase HbFG16D expression.

Methods: Adults with severe SCD, defined by recurrent vaso-occlusive events (VOEs) and acute chest syndrome, were enrolled in this study. All patients received a single dose of IV melphalan (140 mg/m2) before being treated with ARU-1801 gene therapy. Patients were weaned off transfusions 3-6 months after ARU-1801 infusion and were monitored for adverse events, laboratory parameters, and clinical manifestations of SCD. Levels of anti-sickling globin (ASG, composed of endogenous HbF, HbA2 and ARU-1801-derived HbFG16D) are presented as percentages of endogenous hemoglobin.

Results: As of December 2021, 3 patients treated with ARU-1801 have follow-up of >9 months. Vector integration site analysis has shown polyclonal patterns of integration in all 3 patients with no evidence of clonal expansion. A metanalysis of the worldwide experience of autologous HSC gene therapy (Tucci F, et al EHA 2020) showed that over 250 patients have been treated with lentiviral (LV) gene therapies since 2007 without any reports of LV-related insertional mutagenesis. Given the clinically demonstrated safety of LV vector, the intensity of conditioning may be an important factor to reduce the risk of future malignancies. ARU-1801 demonstrated a favorable safety profile with no ARU-1801-related or melphalan-related serious adverse events to date. No cases of hematologic malignancy have been reported. Patients achieved neutrophil engraftment within 7-9 days (median, 7 days) and platelet engraftment within 6-12 days (median, 7 days). Under the initial manufacturing process, P1 has shown stable signs of efficacy, including a VCN of 0.2, expression of 20% HbFG16D and 31% total anti-sickling globin, and 64% F-cells at 2 years. P2 had below-target exposure to melphalan, likely due to rapid clearance of melphalan as a result of renal hyperfiltration. Despite lower engraftment (VCN of 0.1), P2 maintained stable expression of 22% ASG expression and 36% F-cells at 2 years due to sustained increases in endogenous HbF and HbA2. P3 was the first patient treated under the new manufacturing process and has demonstrated a stable VCN of 0.7 (latest measurement at month 9), expression of 27% HbFG16D and 41% ASG at month 10, and 92% F-reticulocytes at month 6, showing near pan-cellular expression of HbF.

Conclusion: Treatment with ARU-1801 has shown remarkable improvement in clinical outcomes. In the 24 months before treatment with ARU-1801, patients had 12-41 VOEs (median, 21) and were hospitalized for 1-7 of those VOEs (median, 6). In the 24 months

after treatment, Patients 1 and 2 have seen 93% and 85% reductions in the number of VOEs, and Patient 3 has had no VOEs through 10 months of follow-up, a 100% reduction. The corresponding total days in hospital associated with those VOEs decreased from 1-91 days (median, 15) to 0-17 (median, 0) after treatment, an average reduction of 93.8%. These results are an encouraging sign of the therapeutic benefit of ARU-1801 with reduced-intensity conditioning for patients with SCD.

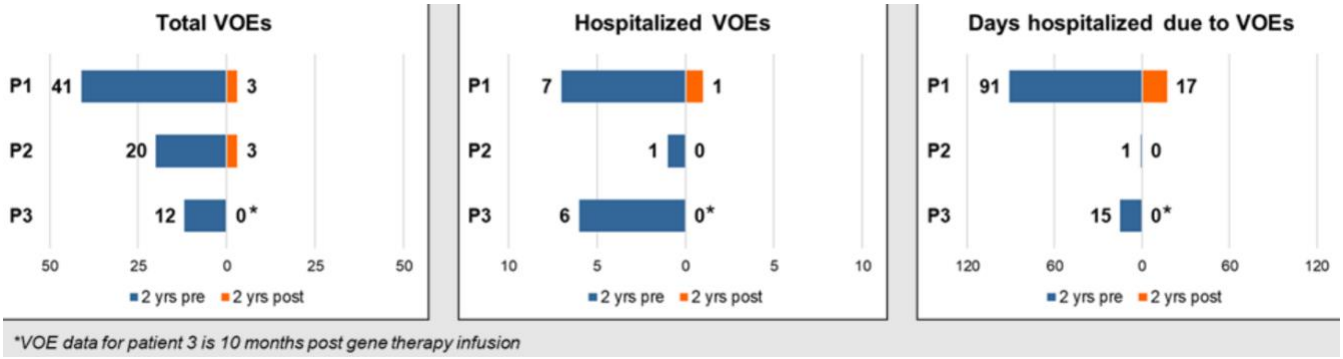


Figure 1. Reduction in vaso-occlusive events (VOEs) and associated hospitalizations (24 months pre-treatment vs 24 months post-treatment)

JSCDH-D-21-1030646

FT-4202, A PYRUVATE KINASE-R ACTIVATOR, DEMONSTRATES PROOF OF CONCEPT IN PATIENTS WITH SCD

Authors: R Clark Brown, MD, PhD[1], Santosh L. Saraf, MD[2], Kimberly Cruz[3], MD, MS, Abdullah Kutlar, MD[4], George Konis, MD[5], Theodosia A. Kalfa, MD, PhD[6], Frans A. Kuypers, PhD[7], Jeremie H. Estepp, MD, Maria D. Ribadeneira, PhD[8], Sanjeev Forsyth, MS[8], Patricia Schroeder, PhD[8], Eric Wu, PhD[8], Patrick Kelly, MD[8], Marilyn J. Telen, MD[9]

Affiliation: *[1]Department of Pediatrics, Aflac Cancer & Blood Disorders Center of Children's Healthcare of Atlanta and the Department of Pediatrics, Emory University, Atlanta, GA, [2]Sickle Cell Center, University of Illinois at Chicago, Chicago, IL, [3]Advanced Pharma, Miami, FL, [4]Augusta University, Augusta, GA, [5]Woodland International Research Group, Little Rock, AR, Cancer and Blood Diseases Institute, [6]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [7]Children's Hospital Oakland Research Institute, Oakland, CA, Departments of Global Pediatric Medicine and Hematology, St. Jude Children's Research Hospital, Memphis, TN, [8]Forma Therapeutics, Inc., Watertown, MA, [9]Department of Medicine, Division of Hematology, Duke University Medical Center, Durham, NC*

Background: The hallmark of sickle cell disease (SCD) is hemoglobin S (HbS) polymerization upon deoxygenation, resulting in red blood cell (RBC) sickling, oxidative damage, membrane damage, hemolysis, cell adhesion, and vaso-occlusion. Exacerbating SCD pathogenesis, the HbS RBC has increased 2,3-diphosphoglycerate (2,3-DPG) with corresponding decreased oxygen affinity, as well as decreased adenosine triphosphate (ATP). FT-4202, a small-molecule allosteric activator of erythrocyte pyruvate kinase (PKR), increases PKR activity resulting in decreased 2,3-DPG levels and increased ATP levels in RBCs.

Methods: FT-4202 is being evaluated in a randomized, double-blind phase 1 study (NCT03815695), which includes cohorts of healthy subjects and patients with SCD, and results have been reported for several cohorts. In healthy subjects, FT-4202 was well tolerated and demonstrated physiologic responses (Kalfa et al. Blood 2019). Further, a cohort of patients with SCD who received a single dose of FT-4202 showed a favorable safety profile for FT-4202 and promising pharmacodynamic effects (Estepp et al. EHA 2020). Cohorts of patients with SCD receiving multiple doses of FT-4202 are currently being studied. We report available data as of 16-Nov-2020, at which time, the first 14-day treatment cohort had completed, but data remain blinded. For analyses of biological effects, patients were classified based on FT-4202 plasma levels to maintain blinding.

Results: In the first 14-day treatment cohort, 9 patients (8 Hb SS; 1 Sβ+ thal) were randomized 7:2 to FT-4202 300 mg once daily or placebo. The median age was 31 years (range: 19 to 43) and the group included 6 women (67%) and 3 men (33%). Six of the 9 patients were on stable hydroxyurea. Fifteen treatment-emergent adverse events (TEAEs) were reported in 7 patients. Most TEAEs (8/15) were grade 1, including headache (n=3) and 1 each of nausea, constipation, somnolence, increased LDH, and increased AST; of these, 1 AE of headache and 1 of nausea were considered possibly related to study drug. Six TEAEs were grade 2 (all unrelated to study treatment): 1 each of nausea, vomiting, and increased reticulocytes, and 3 uncomplicated sickle pain events (in 2 patients). The pain AEs were consistent with each patient's SCD pain history, and all were treated with their standard home pain medications (no SAE/no hospitalization). One patient had a grade 4 TEAE of elevated creatine kinase, unrelated to study treatment.

Levels of RBC 2,3-DPG decreased from baseline and remained at similar levels through the 14-day period

(p=0.031). RBC ATP levels rose more slowly, continuing to increase to day 14 (p=0.031). In treated patients, Hb–oxygen affinity was increased as demonstrated by decrease in the partial pressure of oxygen at 50% Hb saturation (p50) at day 14 (p=0.031), reaching values similar to those of untreated healthy subjects. After 14 days, Hb increased (median 1.2 g/dL, range: 0 to 2.3) with 6/7 patients having an increase of >1 g/dL, and there were decreases from baseline in reticulocyte count (median 60%, range: 39% to 81%), LDH (median 36%, range: +18% to 57%; 6/7 patients had a decrease), and bilirubin (median 35%, range: 7% to 63%).

Conclusion: FT-4202 300 mg once daily demonstrated a favorable safety profile in patients with SCD receiving up to 14 days of dosing. Consequently, the second multiple-dose cohort in patients with SCD has been initiated. FT-4202 300 mg once daily decreased 2,3-DPG levels and increased ATP in RBCs, which correlated with increased RBC oxygen affinity and improved RBC deformability and membrane function. In addition, improvements in hematologic and hemolytic parameters were also observed. Therefore, the study demonstrated proof of concept for FT-4202 300 mg once daily and, based on these results, a phase 2/3 efficacy study is ongoing (NCT04624659).

JSCDH-D-21-1040101

PREVALENCE OF NEURO-DEVELOPMENTAL DEFICITS IN YOUNG CHILDREN WITH SICKLE CELL DISEASE

Authors: Nnenna U. Badamosi, MD, MPH, Gabrielle Walton, MSW, Betty Pace, MD

Affiliation: *Augusta University*

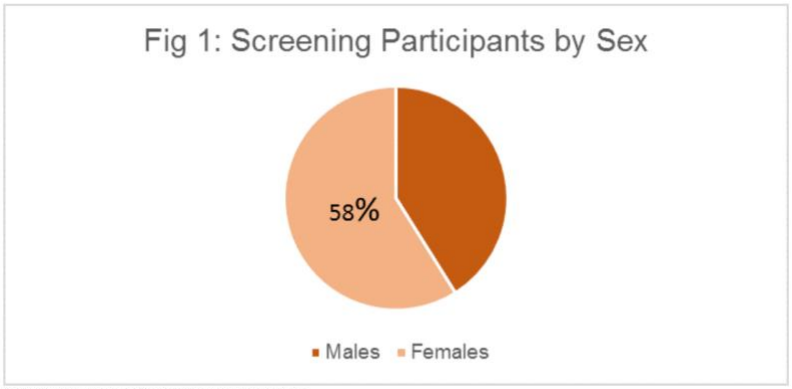
Background: Sickle cell disease (SCD) is an inherited disorder of red blood cells that leads to poor oxygen supply and multi-organ damage. It affects nearly 100,000 Americans, majority of whom are of Black or African American ancestry (CDC, 2020). Neurologic complications include cerebral vasculopathy, silent infarcts and overt strokes which can disrupt normal neurologic development in childhood, and lead to cognitive deficits and disability in adulthood. In addition, young children with sickle cell disease are often dealing with the additional burden of healthcare disparities, socio-economic challenges and inadequate primary care. As a result, many neuro-developmental delays are under-recognized or missed in early childhood. The Parents' Evaluation of Developmental Status, or PEDS group of tests, are evidence-based screening tools for children aged 0 – 8 years that identify parental concerns regarding language, motor, self-help and academic skills as well as socio-emotional and mental health status. These tools can be used to identify developmental delays in children with SCD who may have inconsistent primary care follow up. We sought to describe the neuro-developmental deficits identified in our patient population using these tests.

Methods: The PEDS Developmental Milestone (PEDS: DM) screening test was performed by the social worker during her evaluation at comprehensive sickle cell clinic visits. Screenings were administered routinely to all children with SCD under 60 months (5 years) old, and to children with parent-identified concerns between 5 and 8 years old. Testing took place in person and on campus at the Children's Hospital of Georgia in Augusta, as well as via telephone for children who were seen in the satellite clinics across rural South Georgia (Waycross, Albany, Valdosta, Athens and Dublin). Age-appropriate developmental screening was performed for quarterly milestones in infants (3, 6, 9 and 12 months) and yearly milestones in children over the age of 12 months. Optional Modified Checklist for Autism in Toddlers, or M-CHAT, screening was available for children with parent-identified concerns.

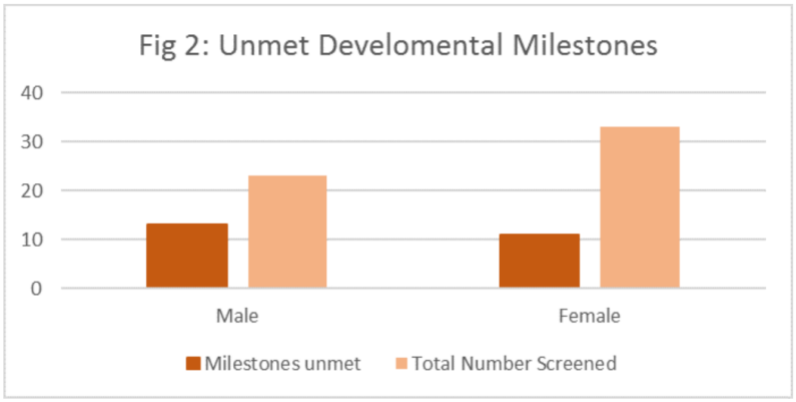
Results: A total of 62 developmental screening tests were performed on 56 children, with 6 children having more than one test. Age range of children who underwent screening was 3 – 50 months (median: 23 months). Thirty-three out of 56 children (58.9%) were females and 23 were males (Fig 1). Fifty-four children identified as African American (96.4%), and the other 2 identified as Hispanic. On review of screening results, 24 out of 56 (42.8%) children had unmet milestones in at least one domain, with 12 children (21.4%) having unmet milestones in 2 or more domains. A sex predilection was noted with 13 out of the 23 male children (56.5%) screened having unmet milestones when compared to 11 of 33 female children (33.3%) (Fig 2).From the population experiencing unmet milestones, the most common deficits were in fine (45.8%) and gross (33%) motor delays. In addition, children experienced delays in expressive language (25%), self-help (20.8%) and social-emotional skills (16.7%) (Fig 3).

Conclusion: Our developmental screening identified a high prevalence of neuro-developmental delays and unmet milestones in young children with SCD, about 43% in our population, with fine and gross motor delays being the most commonly identified deficits. Apart from underlying SCD, male children appeared to be at higher risk than female children for developmental delays. The reasons for this are unknown and beyond the scope of the screening tool. Although our data is limited by small sample size, it highlights the importance of routine developmental screening to identify and manage early neurologic

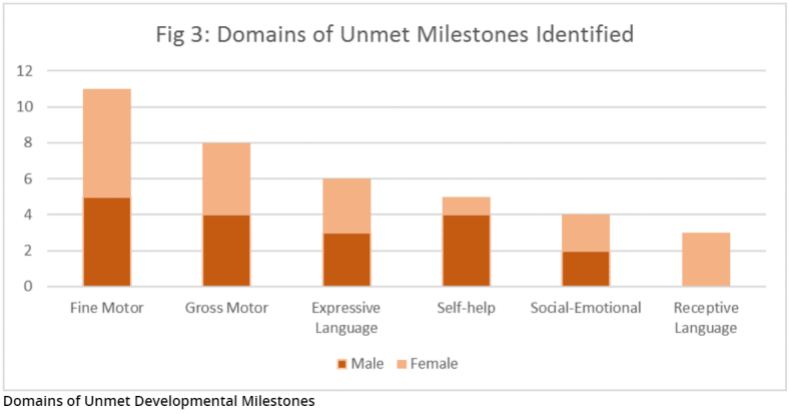
deficits especially in young children with SCD. Future studies should be directed towards assessing factors, if any, that may contribute to higher risk in young boys, and directing appropriate resources to this at-risk population.



Sex Distribution of Screening Participants



Unmet Developmental Milestones in SCD Population by Sex



Domains of Unmet Developmental Milestones

JSCDH-D-21-1048217

RENAL TRANSPLANT IN SICKLE CELL DISEASE: EQUAL OUTCOMES BUT STAGNANT TRANSPLANT RATES

Authors: Kaitlyn C. Dykes, MD[1], Krystsina Miatlovich, BS[2], Basit Javaid, MD, MSC[1], Craig Kessler, MD[1]

Affiliation: *[1]Georgetown University Hospital, [2]Institute of business and management of technologies; IBM*

Background: Sickle cell disease (SCD) treatment has improved, such that more patients are surviving well into adulthood. Yet, this population remains severely impacted by solid organ dysfunction, now the number one cause of morbidity and mortality. Renal failure is most common, due to irreversible damage to the kidneys from complex thrombo-inflammatory mechanisms. Literature supports that solid organ transplant is likely favorable for SCD patients, however there is a void in understanding recent outcomes and overall prognosis in this population since the development of major medical advancements in SCD treatment and renal transplant. Since the year 2000, both SCD treatment and renal transplant were revolutionized by the food and drug administration approval and widespread use of pivotal therapeutics, respectively hydroxyurea and immunosuppressants. At present, clinicians lack updated evidence based research to guide decision making in the treatment of SCD renal transplant recipients. The purpose of this research was to describe the SCD renal transplant population and determine outcomes compared to all African American (AA) patients.

Methods: 2010-2020 United States Renal Data System (USRDS) data was obtained to calculate incidence of SCD end stage renal disease (ESRD) and mortality. Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) 1988-2019 kidney transplant data was obtained and baseline characteristics were determined (Table 1). Kaplan Meier curves not censored for death were created for overall and graft survival between two eras: 2000-2019 and 1988-1999. Apache Spark was used for data analysis.

Results: SCD nephropathy accounted for 0.1% of ESRD incidence, impacting 80-100 patients annually. Incidence of death was 21.7% in the first year after diagnosis. In both eras, SCD patients accounted for 0.3% of all renal transplants. Therefore the rate of SCD related ESRD exceeded the number of patients receiving transplant 9:1. Post 2000, the median SCD renal transplant recipient was 38 years old and 89% were able to perform ADLs. SCD patients had significantly lower Kidney Donor Risk Index (KDPI) than all AA recipients. Of the recent era SCD patients with a known panel reactive antibodies (PRA), < 6% of patients had >0% PRA. SCD renal recipient survival in the current era was not statistically different from all AA patients, P-value= 0.150 (Figure 1). Conversely, overall survival was statistically different pre 2000, P-value= 0.028. In both eras graft survival in SCD patients was not statistically different from all AA patients.

Conclusion: SCD patients with ESRD had a high incidence of death, yet SCD patients continued to account for only 0.3% of renal transplants and the rate of SCD related renal failure exceeded the number undergoing transplant 9:1. Our research showed the SCD renal transplant population as generally young and functional, with equivalent PRA values and lower KDPI scores than the total AA population. SCD renal transplant recipients had equal overall and graft survival compared to AA patients in the current era. These findings suggest SCD patients are suitable transplant candidates, would benefit from transplant and should not be excluded based on SCD status.

	Sickle cell	Other	P-value
	238	78110	
Age, median	38	51	<0.001
Male (%)	55.46	59.41	0.216
BMI median	21	25	<0.001
Dialysis duration, Median, years	3.65	3.98	0.022
Total days on waiting list median	641	636	0.226
Deceased donor N (%)	170 (71.43)	63121(80.81)	<0.001

Table 1
Baseline Characteristics (2000-2019).

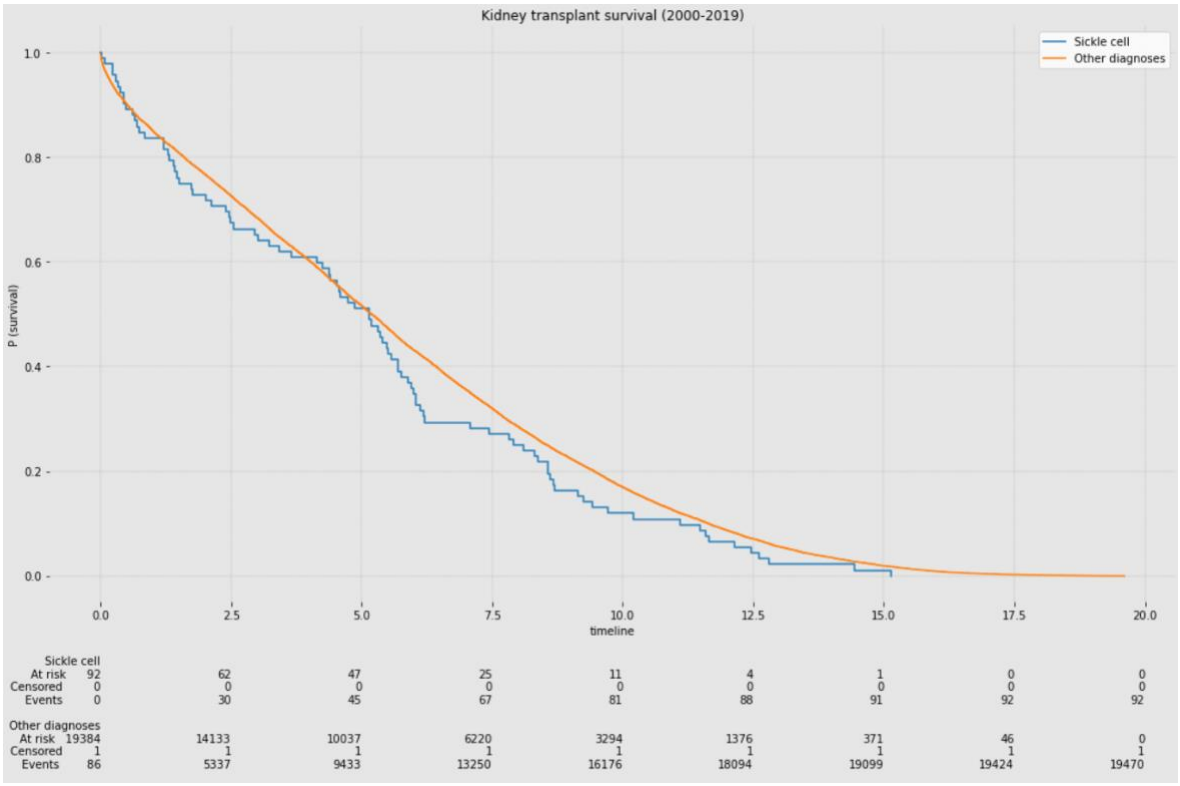


Figure 1
Overall survival of SCD renal transplant recipients (blue line) compared to AA recipients (orange line) post year 2000, P-value= 0.150.

ABSTRACT BREAKOUT SESSION II
BASIC SCIENCE ORAL PRESENTATIONS

Presenting: Sunday, May 30, 2021 at 1:30 PM

JSCDH-D-21-1039953

HEMOPEXIN PREVENTS AND RESOLVES MICROVASCULAR STASIS IN A MODEL OF SICKLE CELL DISEASE

Authors: Thomas Gentinetta[1], Gregory Vercellotti[2], Chunsheng Chen[2], Julia Nguyen[2], Fuad Abdulla[2], Ping Zhang[2], Gregory Kato[3], Nathan Brinkman[4], Adrian Zuercher[1], John Belcher[2]

Affiliation: *[1]CSL Behring AG, Research and Development, Bern, Switzerland, [2]Department of Medicine, Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, Minnesota, USA, [3]CSL Behring, Clinical Research & Development, King of Prussia, Pennsylvania, USA, [4]CSL Behring, Research & Development, Kankakee, Illinois, USA*

Background: Polymerization of hemoglobin-S (HbS) in the deoxy conformation shortens the lifespan of sickle red blood cells and promotes intravascular and extravascular hemolysis. When sickle red blood cells are lysed intravascularly, HbS is released into the vascular space where it can consume nitric oxide and be oxidized to higher oxidative forms. During these reactions, ferric (Fe3+) HbS is formed, which readily releases heme. The released heme can bind to myeloid differentiation factor-2 (MD-2) and activate the innate immune pattern recognition receptor toll-like receptor 4 (TLR4) on endothelium, leading to P-selectin expression, NF-κB activation, and microvascular stasis in sickle cell disease (SCD) mice with implanted dorsal skin-fold chambers (DSFCs). Heme-induced TLR4 signalling and stasis are blocked by administering hemopexin with the heme. Plasma hemopexin has the highest binding affinity for free heme, rendering it relatively nonreactive and delivering it safely to the liver for endocytosis and degradation by heme oxygenase-1 (HO-1). Due to chronic hemolysis, hemopexin levels are depleted in SCD patients and mice.

We previously reported that intravenous hemopexin induces hepatic HO-1 activity and inhibits ongoing, spontaneous stasis in the venules of SCD mice for up to 48 hours. In the current studies, we asked the question how much of the hemopexin-mediated protection is due to preventing heme activation of TLR4 signalling versus induction of HO-1 and CO production. Lastly, we investigated if hemopexin complexed with heme would be as effective as hemopexin alone.

Methods: All animal experiments were approved by the University of Minnesota's Institutional Animal Care and Use Committee. These studies utilized Townes-SS sickle mice on a 129/B6 mixed genetic background. Townes-SS mice with implanted dorsal skin-fold chambers (DSFCs) were anesthetized, placed on an intravital microscopy stage, and 20–24 flowing subcutaneous venules were selected and mapped. After baseline selection of flowing venules, mice were infused with Hb and hemopexin as described below. The same vessels were re-examined for stasis at 1 h or as indicated and percent stasis was calculated.

Results: First, in a stasis prevention model, we intravenously administered different doses of hemopexin in Townes SCD mice with a DSFC one hour prior to a hemoglobin challenge. After baseline selection of flowing venules and one hour after administration of different doses of hemopexin (0 – 160 mg/kg body weight), microvascular stasis was triggered by infusing hemoglobin (1 µmol/kg). The same vessels were re-examined for stasis (no flow) and percent stasis was calculated. Our results show that hemopexin effectively reduced stasis in a dose responsive manner when delivered one hour prior to the hemoglobin challenge.

Second, we evaluated hemopexin in a VOC acute treatment model by infusing various doses of hemopexin 30 minutes after the intravenous hemoglobin challenge. We found a dose-dependent effect of hemopexin to reduce and resolve

microvascular stasis during an acute VOC one hour after hemopexin infusion. We obtained similar results after inducing stasis with lipopolysaccharide (LPS) or hypoxia-reoxygenation in place of hemoglobin challenge.

Third, we evaluated equimolar hemopexin-heme complexes in a VOC acute treatment model by infusing equimolar doses of hemopexin-heme 40 minutes after the intravenous hemoglobin challenge (1 µmol/kg) to further elucidate the effects of heme scavenging versus HO-1 induction. Our results showed a striking, dose-dependent reduction in stasis, albeit to a detectably lower degree than hemopexin free of heme.

Conclusion: Hemopexin has a dose-dependent effect to prevent and treat vaso-occlusion induced in a mouse model of SCD by hemoglobin, LPS, and hypoxia-reoxygenation. This effect is partially replicated by hemopexin pre-complexed with heme, suggesting that the beneficial effect is not limited to clearance of circulating heme. The partial effectiveness of hemopexin-heme complex is consistent with our prior published data implicating CO generation by HO-1 as playing a role in the relief of vaso-occlusion by hemopexin.
We conclude that hemopexin shows promise for the treatment of VOC. Additional experiments are needed to clarify the activity of hemopexin in clearance-dependent and -independent mechanisms of resolution of vaso-occlusion. Clinical trials of hemopexin are warranted to evaluate its safety, tolerability and potential efficacy in relieving vaso-occlusive pain crisis in patients with SCD.

JSCDH-D-21-1039982

PHARMAKOKINETICS OF HEMOPEXIN IN HBSS-, WT-MICE, RATS AND MONKEYS FOR THE TREATMENT OF ACUTE VOC IN SCD

Authors: Gerald Hoebarth[1], Tanja Ruthsatz[1], Joseph Bain[1], Marcel Mischnik[1], Thomas Gentinetta[2], Monika Edler[2], Kirstee Martin[1], Matthias Pelzing[1], Hadi Lioe[1], Kalpeshkumar Patel[1], Daniel Schu[1], Gregory Kato[1], Eva Herzog[1]

Affiliation: *[1]CSL Behring Innovation GmbH, [2]CSL Behring AG*

Background: Sickle cell disease (SCD) is an inherited, autosomal recessive disorder that leads to hemolytic anemia and vascular disease, with a range of acute and chronic complications driven by self-perpetuating cycle of vaso-occlusion and vaso-occlusive crises (VOCs). CSL889, a human plasma derived hemopexin, is being developed as a novel pharmacologic therapy to scavenge cell free toxic heme in patients with VOC, with the goal of reducing the duration and severity of acute VOC in adults and children with SCD.

Methods: In order to evaluate the pharmacokinetics (PK) of CSL889, single-dose PK studies were performed following intravenous (IV) administration in Townes HbSS mice, a model for sickle cell disease, (Hbbtm2(HBG1,HBB*)Tow), wild type C57BL6 (WT) mice and rats at a dose of 35 mg/kg, and in cynomolgus monkeys at doses of 50, 150 and 500 mg/kg BW. Additionally, a PK following repeated dosing (up to 3 repeat doses each 4 hours apart at a dose of 500 mg/kg IV) in Townes HbSS mice was conducted. In addition to CSL889, the concentration-time profiles of hemopexin:heme complex and total heme were described. Townes HbSS mice were used because they express the human HbSS and mimic the major features of the human SCD (eg. sickled red blood cells (RBCs) with a half-life of 2.4 days vs normal RBCs with a half-life of 15.7 days in healthy mice). Quantification of total human hemopexin (CSL889) in mouse, rat and cynomolgus monkey was performed using LC-MS/MS.

Results: In comparison to WT mice, Townes HbSS mice showed a markedly decreased Cmax (0.41 mg/mL vs 0.70 mg/mL) associated with a markedly increased clearance (23.0 vs 1.6 mL/kg/h) and consequently decreased half-life (7 vs 58 h) and mean residence time (MRT; 5 vs 81 h) following IV administration of CSL889. Similarly, the area under the curve (AUC0-inf) was 14-fold higher in WT- compared to Townes HbSS mice (21.8 vs. 1.52 h*mg/mL). PK parameters of CSL889 in rats were comparable to that in WT mice - Cmax (0.74 mg/mL), clearance (1.78 mL/kg/h), half-life (58 h) and AUC0-inf (19.6 h*mg/mL).

For hemopexin, following repeated IV administration, plasma levels accumulated up to the 3rd dose, reached a plateau and declined subsequently over the following 24 hours. AUC0-inf was 345 h*mg/mL, MRT 21.4 h, half-life 13.7 h and IVR 93%. For hemopexin:heme complex, the highest plasma levels were measurable at 5 min after the first dose of CSL889. Levels declined slightly until they reached a steady state after the last dose up to the last timepoint measured. Total heme plasma concentrations first declined slightly and showed an increase to the end of the concentration-time profile (Figure 1).

In cynomolgus monkeys, Cmax and AUC of CSL889 increased slightly less than dose-proportionally over the dose range of 50-500 mg/kg (Cmax from 1.6 to 10.4 mg/mL and AUC0-inf from 84.4 to 587 h*mg/mL). A slightly higher total clearance (Cl) [0.85 vs 0.66 vs. 0.61 mL/h/kg] and a slightly higher volume of distribution at steady state (Vss) [105 (high dose) vs 68 (mid dose) vs 59 mL/kg (low dose)] was observed at the high dose compared to the intermediate and low dose. The terminal half-life following IV administration increased with dose from 80 to 103 h.

Conclusion: Townes HbSS mice tested at 35 mg/kg showed a shorter half-life compared to the healthy rodent species (7 h vs. 58 h) suggesting an increased binding of CSL889 to accessible heme in SCD. Following repeated dosing in Townes HbSS mice increasing hemopexin concentration levels correlate with decreasing total heme plasma levels. The increase of total heme towards the end is most probably due to the saturation of the clearance mechanism and ongoing hemolysis.

JSCDH-D-21-1053315

EFFECT OF MATERNAL CANNABINOID USE ON OFFSPRING'S HEALTH IN MICE WITH SICKLE CELL DISEASE

Authors: Donovan A. Argueta, Ph.D., Raghda Fouda, Ph.D., Christopher Ventura, Ph.D., Stacy Kiven, B.S., Kalpna Gupta, PhD

Affiliation: University of California - Irvine

Background: Cannabis use is rising amongst pregnant women. An estimated 4% of pregnant women in the United States use cannabis, but in California, approximately 20% of 18-24-year-old pregnant women reported using cannabis (Young-Wolff et al., JAMA 2017). Cannabis and cannabinoid use are relatively higher in patients with sickle cell disease (SCD) compared to the general population, perhaps due to pain. SCD patients in the Western world are generally treated with hydroxyurea (HU), but HU is not prescribed during pregnancy, which may increase the likelihood of cannabinoid use to control pain. This may have adverse effects on the offspring's health as even a single dose of synthetic- (CP55,940) or phytocannabinoids (cannabidiol or trans-Δ9-tetrahydrocannabinol) when administered to pregnant C57BL/6 mice on day 8 of gestation produced developmental changes in the offspring. (Fish et al., Sci. Rep. 2019). Thus, we hypothesized that cannabinoid use during pregnancy would have teratogenic effects on the offspring's health in SCD. Using humanized transgenic Berkeley sickle mice, we examined the effect of chronic maternal cannabinoid exposure on the health outcomes of their offspring.

Methods: We paired homozygous (HbSS) BERK males with hemizygous (HbAS) BERK females (homozygous SS BERK females do not breed well). To simulate the human use of cannabinoids, female mice were treated with HU (i.p., 50 mg/kg/d) for two weeks prior to pairing with a male. Female mice were then maintained on a non-selective cannabinoid receptor agonist, CP55,940 (CP; i.p., 0.3 mg/kg/d) or vehicle (Veh; 2% DMSO in sterile saline) during breeding until the pups were born (~3 weeks). At birth, we recorded: [a] litter size, [b] body weight, [c] body size (crown to rump length), [d] right and left eye diameters, and [e] front- and hind-limb lengths using high-resolution digital images for quantification. At post-natal day 21, pups were weighed and euthanized then their organs were collected and weighed.

Results: Observations at birth: Use of HU in HbAS females yielded a larger mean litter size than those of untreated AS females (8.5 vs. 5.5 pups/litter). Body weights of offspring were not significantly changed by any treatments when compared to Veh. Maternal HU+CP treatment significantly reduced crown to rump length in offspring compared to HU-alone ($p< 0.005$). HU+CP effects on offspring crown to rump length were specific to females ($p< 0.002$), whereas male offspring displayed no significant change compared to HU alone. Maternal HU treatment increased right and left front limb size in male and female offspring compared to Veh ($p< 0.001$). HU+CP treatment significantly reduced right and left front limb size in male and female offspring compared to HU alone ($p< 0.001$) and reduced eye size in male offspring ($p< 0.001$) but not female offspring compared to HU treatment alone. Taken together, these data show that maternal cannabinoid treatment leads to significant alterations of physical development in a sex-specific manner.

Observations at post-natal day 21: The offspring of AS/SS mice treated with HU+CP had approximately a 20% decrease in the ratio of brain to body weight compared to HU+Veh treatment ($p< 0.001$), irrespective of sex.

Conclusion: Perinatal exposure to cannabis during pregnancy and lactation has been suggested to be associated with cognitive deficits, emotional disturbances, or affective disorders during childhood and adolescence, in addition to low birth weight and head circumference reduction at birth (Navarrete et al., Front. Psychiatry 2020). As well, maternal cannabis use disorder during pregnancy has been linked with preterm complications, the smaller size relative to gestation age, and increased risk for death within the first year of life (Shi et al., Addiction 2021). Long-term cognitive impacts of prenatal cannabinoid exposure are not fully understood, but evidence from a 22-year longitudinal study indicates impairment of memory function in early adulthood from prenatal exposure (Wilford et al., Neurotox and Teratology 2021). In conclusion, our data suggest that the development/growth of the offspring's body and brain are affected by prenatal cannabinoid exposure.

With the rising use of cannabis and medical cannabis, our observations raise concern for their use during pregnancy in SCD, which may have adverse effects on offspring's health and therefore requires monitoring in prospective clinical studies.

ABSTRACT BREAKOUT SESSION II
HEALTH SERVICES & PSYCHOSOCIAL ORAL PRESENTATIONS

Presenting: Sunday, May 30, 2021 at 1:30 PM

JSCDH-D-21-104256

TIME ALLOCATION AMONG PATIENT NAVIGATORS IN AN ADULT SICKLE CELL MEDICAL HOME

Authors: Wally R. Smith, MD, Shirley Johnson, B.A., L.S.W, Benjamin Jaworowski, B.S.

Affiliation: Virginia Commonwealth University

Background: Patient Navigators (PNs) are community health workers who bridge the gap between patients, communities and health care systems. They are often employed by institutions as utilization managers. PN case management of adults with sickle cell disease (SCD) requires assisting patients not only with the biological ravages of SCD, but also with a plethora of tasks to combat adverse social determinants of health, especially for higher utilizing patients who require utilization management. We studied how PNs allocate their time in an urban SCD program for adult chronic care.

Methods: PNs (2 in 2018, and 3 for much o 2019) were assigned the program's top 50 highest utilizers in 2018, but began managing other patients ad hoc in 2019. Regardless, activities focused on: 1) decreasing LOS, 2) decreasing inpatient admissions; 3) decreasing ED visits;4) decreasing 3 day ED return visits; 5) decreasing overall charges.
Interventions and visit activity included telephone, face-to-face clinic, face-to-face ED, face-to-face inpatient, or face-to-face community. We analyzed time allocation, visit volume and type, and visits/pt for two consecutive years of PN program activity. This analysis covers only a pre-COVID period.

Results: Table 1 shows that 2 PNs contacted 87 mostly female patients in 2018, and 2-3 PNs contacted 163 mostly female patients in 2019. PNs spent around 20 minutes per contact in each of two years of program activity. But as caseload/PN grew, PNs had 3 fewer contacts per year with each patient, translating into over an hour less time per patient. Table 2 shows time was allocated mostly to visits in the hospital and to telephone calls, followed by contacts in ambulatory clinics. Ambulatory contacts actually took longer than in-hospital contacts, which in turn were longer than phone calls.

Conclusion: Pre-COVID time allocation for SCD case management by PNs was predominantly driven by caseload. Fewer contacts and less time per contact occurred as caseload grew. Still, in most cases, about 20 minutes per contact was required. Previously presented successful utilization management outcomes suggest this time allocation may accomplish reduced utilization among high utilizers.

	Contacts per Patient	Average time per contact	Average total contact time per patient	Total Contacts	Total Pts Contacted
2018	12.6	19.0 minutes	235.0 minutes	1094	87
2019	9.5	17.2 minutes	164.1 minutes	1554	163

Table 1:
Patient Navigator patient contacts and time allocated, 2018 and 2019 in the VCU Adult Sickle Cell Medical Home.

	Number of contacts		Minutes per Contact	
	2018	**2019**	**2018**	**2019**
Clinic Visit/ Outpatient	107	168	31.6	26.6
Community	N/A	14	N/A	56.1
Email	6	3	21.4	7.5
ER Visit	48	74	43.1	19.6
Home Visit	13	70	59.0	48.5
Initial Visit/ Intake	11	6	17.7	10.0
Inpatient	382	309	18.0	16.5
Other	25	33	40.2	52.5
Patient Initiated Contact	82	N/A	11.8	N/A
Phone Call - Left Voice mail	28	46	8.8	7.8
Phone Call/ Tele-medicine	275	574	12.1	12.1
Text Message	117	257	10.0	9.0

Table 2:
VCU Adult Sickle Cell Medical Home Patient Navigator contacts and time per contact by site, by communication mode and by initiator, 2018 and 2019.

JSCDH-D-21-1040375

A CHANGE PACKAGE TO IMPROVE PROVIDER ATTITUDES TOWARDS SICKLE CELL DISEASE PATIENTS

Authors: Hadar Keren-Gill, MD, Linelle Campbell, MD, Amrita Mukherj, MD, Clifford Chao, MD, Christine Lu, MD, Kenneth Rivlin, MD, PhD

Affiliation: *Jacobi Medical Center*

Background: Sickle cell disease (SCD) exemplifies systemic racism in health care. For many SCD patients, the worst inequity is the staff's negative attitude when seeking pain care. Too often, they hear the words "sickler," "drug seeker," or "frequent flyer." These depersonalizing and derogatory terms reflect a negative provider attitude. For many, coming to the ED for treatment is a balance between their dignity or their life. Negative provider attitudes directly impact outcomes by delaying care and increasing hospitalizations, complications, and cost. We all want to do what is right. Sometimes our attitudes toward patients are affected by our implicit bias, negative experiences with patients' behavior, and even the institute'sculture -the hidden curriculum.

Our objective was to create a change package derived from quality improvement interventions that improved provider attitudes and could be implemented with minimum resources.

Methods: We searched PubMed for interventions to improve provider attitudes towards individuals with SCD. We reviewed the successful interventions and extracted the minimal clinical actions needed to implement them in any clinical setting.

Results: We found 64 papers with the search terms "sickle cell" and "attitudes." Of these, we choose two key papers to define our change package.1,2 One centered on using video of patient and provider stories () to personalize individuals with SCD. The other had medical students analyze a typical but stigmatizing provider note to recognize implicit bias.

Our change package is shown in table 1.

Two potential outcome measures for this change package include:

1. Change in positive provider attitude for SCD scale[3]
2. Increased patient confidence that they will always be treated with dignity and respect

Table 1.

Core Element (Driver)	Clinical Activity	Tools
Humanizing Patients	Telling Patient Stories in conferences or other educational venues	Video: "they don't believe me"
Recognizing Implicit Bias	Analysis of stigmatizing clinical note	Do Words Matter? Stigmatizing Language and the Transmission of Bias in the Medical Record[2]

Conclusion: Implementation of change is hard, requiring resources, time, effort, leadership commitment. We believe this change package for improving provider attitude towards sickle cell disease patients is simple, doable, and should be implemented where SCD patients are treated.

JSCDH-D-21-1039719

UNDERSTANDING LYRICAL EXPRESSION: SONGWRITING THEMES IN PEDIATRIC SICKLE CELL DISEASE

Authors: Jaime Kennington, MMT, MT-BC[1], Crystal Weaver, LPC, CRC, MT-BC[2], Tracie Sandheinrich, MA, PLPC, MT-BC[1]

***Affiliation**: [1]Maryville University, [2]Saint Louis University*

Background: Therapeutic songwriting (defined as the process of creating, notating, and/or recording lyrics and music by the client and therapist within a therapeutic relationship to address psychosocial, emotional, cognitive, and communication needs of the client) is emerging as an effective music therapy intervention. Unfortunately, there is a lack of research surrounding common lyrical themes from therapeutic songwriting sessions involving clients who are undergoing active treatment for sickle cell disease and are specifically between 7 and 11 years of age (i.e. Piaget's Concrete Operational Stage).

The objective of this study is to determine if common lyrical themes emerge during therapeutic songwriting sessions with clients who are: 1) undergoing active treatment for sickle cell disease and 2) between 7 and 11 years of age.

Methods: The study involved the retrospective analysis of lyrics from 20 songs created during therapeutic songwriting sessions with board-certified music therapists. Purposive sampling was used to gather song lyrics within a secure database. Content analysis methodology was utilized. Lyrics were coded and categorized into broad themes to summarize data. To ensure rigor, trustworthiness, and credibility of data analysis procedures; the study team first independently conducted the data coding and theme formulations and then met to reach final consensus of themes. Analysis procedures were systematically applied, and an audit trail was maintained to ensure all analysis steps could be traced back to original song lyrics.

Lyrics from songs utilized for the study were created by clients from a university funded, non-profit therapeutic songwriting program in the Midwest. Demographic information for these clients included: (a) 35% (n=7) self-identified as male and 65% (n=13) self-identified as female; (b) 25% (n=5) were 7 years of age, 15% (n=3) were 8 years of age, 30% (n=6) were 9 years of age, 10% (n=2) were 10 years of age, 20% (n=4) were 11 years of age; and (c) 100% (n=20) were undergoing active treatment for sickle cell disease.

Results: The most common lyrical themes for participants who self-identified as male (with frequencies) were: 1) resilience (49%), 2) support systems (13%), 3) negative emotions focused on the treatment process (11%), 4) self-identity (10%), and 5) physical pain perception (9%). The most common lyrical themes for participants who self-identified as female (with frequencies) were: 1) support systems (36.31%), 2) resilience (31.84%), 3) negative emotions focused on the treatment process (10.61%), 4) physical pain perception (8.38%), and 5) diagnosis/treatment process (6.15%).

Results from the study indicate that the three most common lyrical themes generated during therapeutic songwriting sessions with clients (regardless of gender) who are in the Concrete Operational Stage (i.e. 7 to 11 years of age) and are also undergoing active treatment for sickle cell disease are: 1) resilience, 2) support systems, and 3) negative emotions focused on the treatment process. In addition, results from the study indicate that both males and females in the Concrete Operational Stage generated lyrical themes focused on physical pain perception at almost the same frequency.

Conclusion: Findings from this study indicate that individuals between the ages of 7 and 11 years (i.e. Concrete Operational Stage) focus on: 1) their support systems, 2) their perspectives on resilience,

and 3) their negative emotions while undergoing treatment for sickle cell disease (as evidenced by lyrical themes during therapeutic songwriting sessions with board-certified music therapists). Support systems involve the networks (i.e. family members, friends, loved ones, medical staff, and pets) who provide clients with practical and/or emotional support during the treatment process. Resilience involves the capacity to recover quickly from the physical, psychosocial, and emotional difficulties during the treatment process. Negative emotions surrounding the treatment process involve the natural, instinctive state of mind deriving from the clients' circumstances, mood, and/or relationships with others.

This research improves clinical practice by informing healthcare professionals regarding common themes that may arise during sessions with clients undergoing active treatment for sickle cell disease between the ages of 7 and 11 years. Understanding and potentially predicting these common themes allow healthcare professionals to effectively implement interventions (such as therapeutic songwriting) which can assist clients with strengthening the positive components of the active treatment process (such as support systems and resilience) while also appropriately processing the negative components (such as physical pain perception and negative emotions) surrounding the active treatment process.

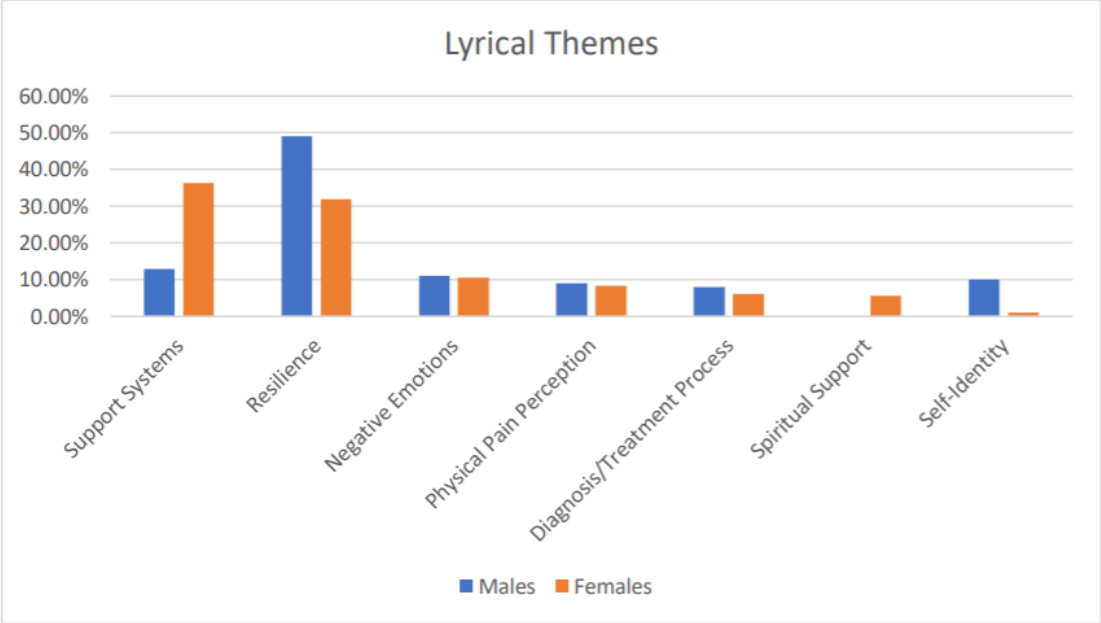


Figure 1:
This table represents the common lyrical themes for both males and females (ages 7 to 11 years)

JSCDH-D-21-1052142

A BEHAVIORAL RISK/ANTICIPATED BEHAVIORAL HEALTH NEEDS SCALE FOR ADULT SICKLE CELL PATIENTS

Authors: Benjamin Jaworoski B.S., Rachel Walls MSW, Shirley Johnson B.A. L.S.W, Wally R. Smith MD

Affiliation: Virginia Commonwealth University

Background: Behavioral health needs of adults with sickle cell disease (SCD) vary, and are influenced by a complex mix of determinants. Adult SCD centers would benefit from an estimate of anticipated behavioral health needs for their populations, that could suggest how best to advocate for and deploy center behavioral health resources. We therefore quantified anticipated behavioral health intervention needs for adults with SCD in one adult center, using an empirically derived scale.

Methods: To derive the scale, a multidisciplinary care team including a researcher developed a list of potential predictors of anticipated behavioral health risk/needs, using formal behavioral health diagnoses found in the claims of 553 subjects (60% F) in the VCU Adult Sickle Cell Medical Home, as well as scores on validated assessment surveys of these patients. The team used presence or absence of each predictor to construct a weighted needs score. Weights were assigned empirically by the team behavioral health specialist and an analyst, according to estimated utilization risk (and need). When patients were dually diagnosed, (e.g., with both a mood disorder and a substance use disorder), extra weight was assigned. The total scale score was the sum of criterion scores.

Results: Table 1 shows the scale criteria used and the point values for each criterion score. The maximum possible scale score was 31.25. The criteria and score weights were shown to clinicians on the team and were generally considered to have face validity. Patients were then assigned risk/need categories according to their scale scores, based on the distribution of the scale scores in the Adult Medical Home sample.

Table 2 shows the risk categories, their associated assigned score ranges and percentile scores, and utilization data from 2020 for the sample. The mean behavioral risk/needs score was 2.48 for the 50 highest utilizers, and the median was 1.25. In contrast, the mean score was 0.74 for 502 other patients (missing =1), and the median was 0. Table 2 also shows progressively increasing ED use per 1000 and inpatient admissions per 1000 according to need/risk category.

Conclusion: We constructed a scale and categories of behavioral risk/anticipated behavioral health needs for adult sickle cell patients that has face validity and construct validity based on utilization over one year. Our long-term goal is further validation of this scale as part of a predictive risk/needs model. We envision using anticipated risk/need to advocate for adult SCD care resources as well as to allocate and deploy resources.

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Element	Name	Point
1	**Mood disorder**	1
	a. ICD-10 dx in past two years OR	
	b. PHQ-9 score of ≥10	
2	**Anxiety disorder**	1.25
	a. ICD-10 dx in past two years OR	
	b. GAD score of ≥10	
3	**Psychotic disorder (ICD-10 dx in past two years)**	2
4	**Personality/behavioral disorder (ICD-10 dx in past two years)**	3
5	**Alcohol use disorder**	3
	a. ICD-10 dx in past two years OR	
	b. Positive AUDIT-C score based on gender	
6	**Sedative, hypnotic, or anxiolytic related disorder (ICD-10 dx in past two years)**	3
7	**Cocaine-related disorder (ICD-10 dx in past two years)**	3
8	**Stimulant-related disorder (ICD-10 dx in past two years)**	3
9	**Drug Abuse Screening Test-10 Assessment score ≥3, no disorder diagnosed elsewhere**	3
10	**Dual behavioral diagnoses**	4
	a. Patient has a single point in elements 1-4 AND	
	b. Patient has a single point in elements 5-9	
11	**Suicide/suicidal ideation in previous two years**	5
	a. Pt has suicide alert in Cerner in past two years OR	
	b. Positive report of suicide attempt/suicidal ideation in assessments	

Table 1: Anticipated Behavioral Needs: Criteria, criterion scores for the anticipated behavioral risk/need scale, Virginia Commonwealth University Adult Sickle Cell Medical Home

Risk Category (score range, percentile score)	N	ED Visits	ED Return 3 days	Inpt DC's	LOS	Inpt Return 30 days	ED Use Per 1000	ED Return Rate	Inpt Adm Per 1000	ALOS	Inpt Return Rate (%)
All	**553**	**1226**	**199**	**397**	**2176**	**56**	2217.0	16.2%	717.9	5.5	14.1
Zero	371	480	36	158	799	22	1293.8	7.5%	425.9	5.1	13.9
Low (1 pt, 70th)	41	69	8	34	291	5	1682.9	11.6%	829.3	8.6	14.7
Med (>1 -2.25, 71st-90th)	98	377	64	130	669	20	3846.9	17.0%	1326.5	5.1	15.4
High (>3.35-4, 91st - 95th)	15	113	43	17	75	2	7533.3	38.1%	1133.3	4.4	11.8
Very High (>4-7.25, 95th-97th)	12	82	27	22	140	5	6833.3	32.9%	1833.3	6.4	22.7
Extremely High (>7.25, >97th)	15	105	21	36	292	2	7000.0	20.0%	2400.0	8.1	5.6

Table 2: Anticipated Behavioral Needs: Behavioral risk/need categories, score ranges, percentiles scores, and utilization outcomes for 2020, Virginia Commonwealth University Adult Sickle Cell Medical Home. ED= emergency department; Inpt=inpatient; LOS=length of stay; Adm=admissions; ALOS=average length of stay; Med= medium.

POSTERS

JSCDH-D-21-1039068

A CASE OF PRIAPISM IN A PATIENT ON VOXELOTOR

Authors: Sherraine Della-Moretta, MD, Payal Desai, MD

Affiliation: *Ohio State University*

Background: Voxelotor is a hemoglobin S polymerization inhibitor approved in November 2019 by the FDA for use in patients with sickle cell disease (SCD) based on increase in hemoglobin. Given its relatively recent approval, more needs to be discovered regarding potential adverse events.

Methods: N/A

Results: A 27-year-old male with sickle cell anemia who presented to the emergency department with 5 hours of priapism. At the time of presentation, his labs show an unremarkable chemistry with liver function tests, including bilirubin, within normal limits. His complete blood count is notable for a white blood cell count of 6.65, hemoglobin of 11.0, and platelets of 386. Home medications include 2000 mg daily of hydroxyurea, 1500 mg voxelotor daily, and 1 mg of folic acid daily in addition to as needed pain medications. He is placed on a hydromorphone pump for pain control without much relief. Approximately 5 hours after presenting to the emergency department, urology performs aspiration of 150 mL of ischemic blood along with phenylephrine injection with resolution of priapism. He is admitted for pain crisis and treated with IV pain medications along with continuation of his home medications. He is discharged on hospital day 3.

At his hospital follow up visit, he notes that he has been having increased episodes of priapism up to 2 to 3 times per week since starting voxelotor for approximately 4 months prior to presentation and correlating to the start of voxelotor. Childhood complications of his sickle cell include acute chest syndrome, leg ulcers, and deep venous thrombosis. While he did also have a history of priapism as a child, this was no longer typical for him in his 20s. On review of his labs, it is noted that his baseline hemoglobin prior to starting voxelotor was around 7 and had increased to approximately 11. His baseline absolute reticulocyte count decreased from around 0.3 million per microliter to 0.16 million per microliter after starting on voxelotor. Despite the priapism, the patient did not want to discontinue voxelotor completely due to resolution of his leg ulcers, feeling much improved in terms of energy, and decreased pain on the therapy. He also stated this is why he hesitated to share the episodes of priapism with the medical team prior to the hospital presentation. After a discussion with shared decision making, his voxelotor was therefore decreased until symptoms of priapism resolved, which occurred at a dose of 500 mg daily. His new baseline hemoglobin with dose modification is ~ 9 g/dl. He reports near resolution of priapism episodes with prompt resolution with medication treatment.

Conclusions: This case highlights an important part of monitoring patients with sickle cell disease who start disease modification with voxelotor. The patient certainly noted a significant improvement in pain, energy, and his quality of life. However, the significant and robust response in hemoglobin also led to episodes of priapism due to the significant hemoglobin increase. We, therefore, recommend close monitoring of hemoglobin at regular intervals at the initiation of medication. For patients with hemoglobin improvement to greater than 10g/dl, we recommend monitoring for signs of hyperviscosity with direct patient questioning. Additionally, in patients who present with new onset of symptoms of hyperviscosity, such as priapism, we recommend shared decision-making on future dosing of voxelotor.This case highlights an important part of

monitoring patients with sickle cell disease who start disease modification with voxelotor. The patient certainly noted a significant improvement in pain, energy, and his quality of life. However, the significant and robust response in hemoglobin also led to episodes of priapism due to the significant hemoglobin increase. We, therefore, recommend close monitoring of hemoglobin at regular intervals at the initiation of medication. For patients with hemoglobin improvement to greater than 10g/dl, we recommend monitoring for signs of hyperviscosity with direct patient questioning. Additionally, in patients who present with new onset of symptoms of hyperviscosity, such as priapism, we recommend shared decision-making on future dosing of voxelotor.

JSCDH-D-21-1039879

ACUTE HYPER-HEMOLYTIC CRISIS WITH THE ABRUPT CESSATION OF VOXELOTOR THERAPY: RETROSPECTIVE

Authors: Shelsie Lindor, Payal Desai, MD

Affiliation: *Ohio State University*

Background: Voxelotor is a medication recently approved for treatment of Sick Cell Disease as it functions to inhibit the polymerization of Hemoglobin S, thus preventing the sickling of red blood cells. This drug has helped improve anemia in patients with sickle cell and may improve manifestations of sickle cell hemolytic complications. As the medication is novel, there is a paucity of data on the cessation of therapy. We present a case with inadvertent abrupt cessation of therapy for a patient with sickle cell disease and clinical manifestations.

Methods: For this case report data was collected retrospectively through the electronic medical record of one sickle cell patient seen in the inpatient setting for sickle cell crises. We compared the markers of hemolysis in the setting of abrupt cessation versus re-initiation of voxelotor.

Results: A 36-year-old African American adult with sickle cell disease (SS) with a history of Acute Chest Syndrome, leg ulcers, and AVN w/ hip replacement presents with an acute vaso-occlusive crisis (VOC). The patient was previously on Hydroxyurea therapy alone at the maximum tolerated dose but reported ongoing fatigue and intermittent leg ulcers. Given her baseline Hb of 7-8g/dL, the patient was started on voxelotor in March 2020. Since the addition of voxelotor, the patient subjectively reported a decrease in overall baseline pain. Additionally, the patient noted eight hospital admissions in 2019 compared to three in 2020 for pain crises. However, during the three hospital admissions in 2020 since the patient started voxelotor, a more profound hemolytic anemia was noted as the patient did not always have the medication at the time of admission. Figures 1, 2, 3 note markers of hemolysis collected, specifically total bilirubin, reticulocyte count, and LDH. Over the course of each hospital admission, we make note of the date that the patient was re-started on voxelotor once brought in from home. Subsequently, we observed a decrease in hemolytic marker levels.

Conclusions: This case demonstrates the impact of voxelotor in a single patient. The medication helped improve baseline hemoglobin as well as patient healthcare utilization. However, the abrupt withdrawal caused significant hyperhemolysis that is much more severe when compared to other prior episodes of VOC. We theorize that abrupt cessation led to an increase in acute sickling and an increase in hemolytic parameters. We caution against abrupt withdrawal of the medication, increased patient education about abrupt cessation, and urge for universal availability of voxelotor on hospital formularies for patient safety.

Figure 1. Total Bilirubin as a marker of hemolysis during Hospital Admissions for Sickle Pain Crisis in 2020.

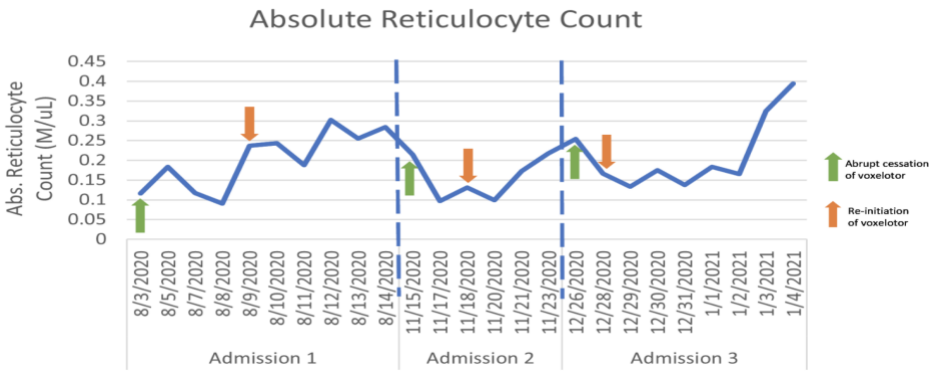


Figure 2. Reticulocyte Count as a marker of hemolysis during Hospital Admissions for Sickle Pain Crisis in 2020

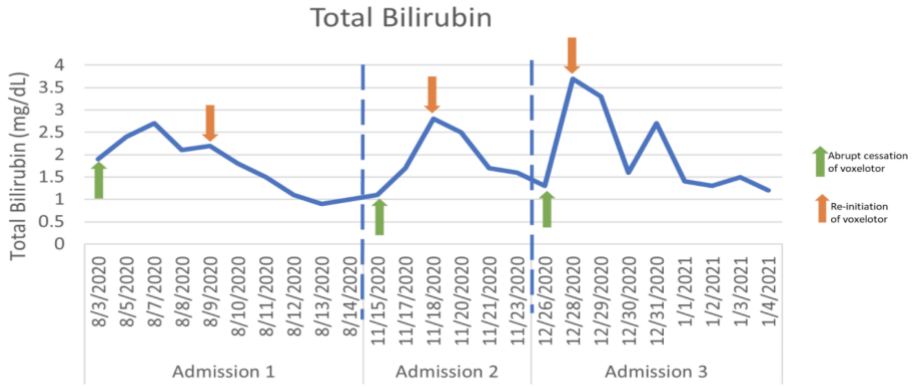
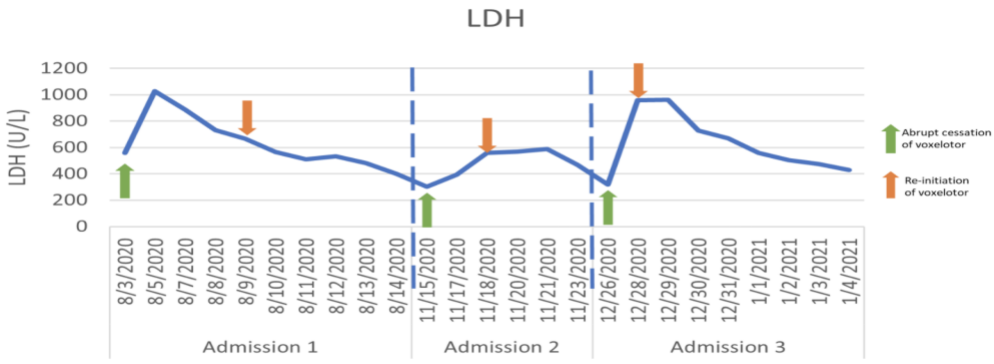


Figure 3. LDH as a marker of hemolysis during Hospital Admissions for Sickle Pain Crisis in 2020



JSCDH-D-21-1040390

ADHESION TO VCAM-1 AND P-SELECTIN PREDICT TIME-TO-RESOLVE (TTR) OF VASO-OCCLUSIVE CRISIS

Authors: Michael Tarasev, PhD[1], Xiufeng Gao, MD[1], Jennell White, PhD[2], Patrick Hines, PhD [1]

Affiliation:[1]*Functional Fluidics Inc.,* [2]*Wayne State University*

Background: Sickle cell disease (SCD) is characterized by frequent and unpredictable vaso-occlusive crises (VOCs) resulting in increased morbidity and mortality. There are no reliable biomarkers to predict the onset and progression of VOCs, complicating disease management. Cell-to-endothelium adhesion at P-selectin and VCAM-1 was shown to significantly contribute to VOC events.

Methods: Standardized, flow-based adhesion bioassays measuring whole blood adhesion to VCAM-1 and P-selectin were used in a 6-month longitudinal study with blood samples collection from SCD subjects every 3 weeks at baseline and during VOC with patient-reported VOC events and return to steady state captured by e-diary. Time-To-Resolution from VOC (TTR) was defined as that reported within one week of the preceding VOC.

Results: Flow Adhesion to P-Selectin during VOC and to VCAM-1 at baseline strongly correlated with TTR with about 50% predictive value; increased to 68% for a combination of these two markers. Inflammatory mediators (e.g. interleukins) and reticulocytes (%), combined with [these biomarkers further increased the multi-parametric model predictive value up to 75-80%. Notably, adhesion on P-Selectin at baseline and on VCAM-1 at VOC lacked significance for predicting TTR.

Conclusions: Times-to Resolution of VOC were found to be highly patient-specific and linked to patient ' blood biochemical and hemodynamic properties. Within study limitations related to the sample size and VOC-related interventions, the data indicate that VOC resolution time can be predicted with the use of flow adhesion and biochemical markers. If validated, such combinations can be utilized for adapting and selecting treatments best suitable for individual patients.

ARDENT PHASE 2B PLACEBO-CONTROLLED TRIAL OF IMR-687 IN PATIENTS WITH SICKLE CELL DISEASE

Authors: Jo Howard, MB, BChir, MRC, FRCPath[1], Rahul Ballal[2], Kenneth Attie[2]

Affiliation: *[1]Guy's and St. Thomas' Hospital, London, UK, [2]Imara, Inc*

Background: Imara is a clinical-stage biopharmaceutical company dedicated to developing novel therapeutics to treat patients suffering from rare inherited genetic disorders of hemoglobin, including sickle cell disease (SCD). Imara's first investigational compound, IMR-687, is being evaluated as an oral, once-a-day, small molecule treatment for SCD and β-thalassemia. IMR-687 is a highly selective, potent inhibitor of phosphodiesterase-9, or PDE9, which modulates cGMP-dependent pathways that can increase fetal hemoglobin (HbF), decrease red blood cell (RBC) hemolysis, inhibit adhesive cell interactions in blood vessels, and promote vasodilation. This could potentially reduce acute and chronic pathology seen in SCD, including vaso-occlusive crises (VOCs), local tissue hypoxia, inflammation, and vascular injury.

IMR-687 has been evaluated in preclinical studies, a Phase 1 clinical study in healthy volunteers, a completed Phase 2a clinical trial in 93 adults with SCD, an ongoing Phase 2a open label extension (OLE) trial (clinicaltrials.gov NCT04053803) in 24 adults with SCD, and an ongoing Phase 2b clinical trial in adults with beta-thalassemia ("Forte," NCT04411082, planned N=120). Pediatric studies in SCD are also planned.

For all IMR-687–treated subjects in the Ph-2a trial, the most common treatment emergent adverse events (subject incidence ≥20%) were sickle cell anemia crisis, headache, and nausea, at doses ranging from 50 mg to 200 mg once-daily. Patients in the OLE trial are currently receiving 200 mg once-daily, which is to be increased to 300 mg or 400 mg, consistent with the higher dose group in the ongoing Phase 2b studies.

The "Ardent" Phase 2b clinical trial (NCT04474314) was initiated in 2020 for the treatment of adults with SCD and is currently enrolling patients; interim data from this trial is expected to be reported in the second half of 2021. The goal of these studies is to leverage IMR-687's differentiated mechanisms of action, its ease of administration, and stable drug properties to potentially serve a broad range of patients suffering from hemoglobinopathies including sickle cell disease around the world, including those in underserved regions.

Methods: The Ardent Phase 2b clinical trial is a global, randomized, double-blind, placebo-controlled, multicenter study of approximately 99 patients, aged 18 to 65 years with SCD and 2 to 12 VOC episodes within the 12 months preceding enrollment. Enrollment is planned across approximately 50 sites and 13 countries. Patients who are receiving a stable dose of hydroxyurea (HU) as part of their established treatment plan are eligible for enrollment. Patient randomization is stratified by use of HU as well as by region. The study will evaluate two dose levels of IMR-687 versus placebo. The lower-dose IMR-687 arm will be dosed at 3.4 to 5.0 mg/kg (either 200 or 300 mg) while the higher-dose arm will be dosed at 5.0 to 6.7 mg/kg (either 300 mg a 400 mg).

The primary efficacy objective of the Ardent trial is to evaluate the proportion of patients with HbF response, defined as an increase of ≥3% in HbF from baseline to week 24, in the IMR-687 treated group(s) compared to placebo. The key secondary objective is the annualized rate of VOCs. Other secondary endpoints include %age F-cells, total hemoglobin, quality of life, and biomarkers of hemolysis, adhesion, and inflammation. While the primary efficacy endpoint for the trial will assess results after 24 weeks

of treatment, patients will continue assigned treatment through 52 weeks to provide data for secondary endpoints, including the annualized incidence of VOCs. Following the completion of 52 weeks of dosing in the trial, patients may be eligible to enroll in an open-label extension study.

Results: An interim analysis is expected to be performed in the second half (H2) of 2021, with the final analysis in H2 2022.

Conclusions: The Ardent clinical study is evaluating the efficacy and safety of IMR-687 as a potentially disease-modifying treatment in adult patients with SCD. The study is currently enrolling participants; further information is available at www.imaratx.com and clinicaltrials.com, NCT04474314.

JSCDH-D-21-1040301

BLOOD DEMAND AND CHALLENGES FOR PATIENTS WITH B-THALASSEMIA MAJOR IN EASTERN SAUDI ARABIA

Authors: Muneer H. Albagshi, MD[1], Nawal Eltayeb[1], Mona Saad[1], Randa Adel[1], Sami Bahjat[2], Abdulaziz Bushehab[1], Abdulmohsen Aljassem[1], Hakemah Alkhamis[1]

Affiliation: [1]*Hereditary Blood Disease Center,* [2]*Maternity and Children Hospital*

Background: The β-thalassemias major is a hereditary disorder of hemoglobin (Hb) which results in defective Hb synthesis leading to chronic severe anemia the mainstay of its treatment is life-long regular packed red cell transfusions accompanied by iron-chelating therapy. Globally there is a gap between blood donation and the actual need of the patients who are depending on transfusion, patients with β-thalassemias major are not an exception and many of them have limited access to regular and safe blood transfusions. In this study, we aimed to assess the gap between demand and supply of blood for transfusion-dependent patients with β thalassemia major treated at hereditary blood diseases center –Al Ahsa Eastern Saudi Arabia.

Methods: The total number of patients on chronic transfusion 158 patients. The adults account for (65%) and the rest are the pediatric population (35%). The total number of units requested during the three years is 14509 units and the total number of received units is 9530 which indicates a gap of 4979 (34%) units. Age of most of units received is more than 7 days: 2017 (36.7%),2018 (49,9%),2019 (61.5%). The rare blood groups and alloimmunization account for less than 8% of the patients. Prestorage filtration is the policy for all the units.

Results: The total number of patients on chronic transfusion 158 patients. The adults account for (65%) and the rest are the pediatric population (35%). The total number of units requested during the three years is 14509 units and the total number of received units is 9530 which indicates a gap of 4979 (34%) units. Age of most of units received is more than 7 days: 2017 (36.7%),2018 (49,9%),2019 (61.5%). The rare blood groups and alloimmunization account for less than 8% of the patients. Prestorage filtration is the policy for all the units.

Conclusions: We suggest rising awareness of thalassemia major demands for fresh blood components, encouraging voluntary blood donations, enhancing national blood banking policies, and reducing fragmentation of blood services to reduce this gap between demand and supply.

JSCDH-D-21-1039959

EDUCATION TO IMPROVE ACCEPTANCE OF COVID 19 VACCINATION FOR SICKLE CELL PATIENTS

Authors: Darla K. Lilles, MD, Chelsea Rivenbark, NP II, Lynne Bair

Affiliation: *Brody School of Medicine*

Background: Since the beginning of the COVID 19 pandemic, it has become apparent that African American individuals have a higher risk of poor outcomes with COVID 19 infections. Patients with Sickle Cell Hemoglobinopathies are no exception and have been shown to have a greater than two-fold increase in mortality from an active COVID infection than their white non-Hispanic counterparts. Despite these high risks, African American patients have a much greater hesitancy to receive COVID vaccination.

Methods: We utilized CDC COVID 19 community-based organization slide deck and scheduled a series of Webex based educational sessions. In addition to the side deck education, patients heard the experiences of two to three vaccinated African American individuals and participated in a question and answer session. At the end of the Webex session, patients were offered an appointment at a vaccination clinic, held at a historically black church in the community, sponsored by the University. There were eight patient attendees at the first session, and two at the second session.

Results: Of the eight patients who participated in the initial educational Webex, three received their vaccines the following week at the vaccine clinic sponsored by the University. Based on survey results, completed by six of the eight participants, half of respondents decided to receive their vaccine, and the other half had still not decided. None of the participants made the decision not to receive their vaccine. Half of the patients felt it helpful to hear the experiences of African Americans who received the vaccine, and two thirds found it helpful to hear the experiences of a sickle cell patient who received the vaccine. Five of the six participants felt the educational Webex was helpful. Of the five that did not receive their vaccine following the initial educational session, two returned for the second educational session.

Conclusions: Survey results, and vaccinations, indicate that targeted education on the COVID vaccine for sickle cell patients is well received by patients and leads to increased COVID vaccination rates among this population. Limitations to this study included small sample size, both in patients who had up to date email addresses in the electronic health record, and in number of session participants.

JSCDH-D-21-1053171

FEEDBACK FROM SICKLE CELL PATIENTS AND CAREGIVERS AFTER TRANSITIONING TO ADULT HEALTHCARE

Authors: Barbara J. Speller-Brown, DNP, CPNP-BC, MSN, Stefanie Marguiles, MS, Brittany Proctor-Moffitt, MSW, LICSW, Petrona Williams, BSN, Andrew D. Campbell, MD, Brenda M. Martin, PNP-BC, MSN,

Affiliation: *Childrens National Hospital*

Background: Landmark advances in pediatric sickle cell care have resulted in children with sickle cell disease (SCD) surviving into adulthood and has increased to 95% by the age of 18. However, there is an abrupt rise in mortality rates between 20 to 24 years of age, and it is usually within 1-2 years after transfer to adult care. Transition is a time when continuity of care is essential to prevent high rates of morbidity and mortality in young adults.

Purpose: This descriptive study evaluated patients and parents/caregivers feedback of the health care transition experience after transition to adult care by post-assessment transition questionnaires and feedback surveys.

Methods: We surveyed sickle cell patients 20-21 years of age at Children National Hospital who transitioned from pediatric to adult care. Feedback surveys and post-assessment feedback questionnaires were conducted with patients who attended the Sickle Cell Adolescent and Young Adult Transition clinic (SCAT). Post-assessment feedback questionnaires were conducted with patient who did not attend SCAT. Data was analyzed using descriptive statistics.

Results: 59 youth with SCD attended the Sickle Cell Adolescent and Young Adult Transition Clinic (SCAT) and 15 did not attend from January 2018- January 2021.59 total youth had Hb SS disease. Of those who attended SCAT 71 % felt prepared to change to an adult provider with 78 % having seen their identified adult heath care provider since leaving pediatric care

Conclusions: Patients enrolled in SCAT receive standardized education, resources and social work services during each clinic visit. In addition, patient's readiness to transition is assessed at each visit utilizing the GOT transition readiness assessment and feedback surveys for both patient and parent/caregiver. Our goal was to determine how well the SCAT clinic prepared patients for transition and to determine if interventions are needed post transition to help patients successfully integrate into adult hematology care.

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HBB HAPLOTYPES AND HBG2, BCL11A, HBS1L-MYB AND BGLT3 SNPS IN SCD CHILDREN FROM ANGOLA

Authors: Miguel Brito[1], Mariana Delgadinho, Catarina Ginete[2], Brigida Santos[3]

Affiliation: [1]*Medicine Instituto Politécnico de Lisboa Escola Superior de Tecnologia da Saúde de Lisboa,* [2]*H&TRC- Health & Technology Research Center, ESTeSL- Escola Superior de Tecnologia da Saúde,* [3]*Instituto Politécnico de Lisboa, Lisbon, Portugal, Centro de Investigação em Saúde de Angola (CISA), Bengo, Angola*

Background: Sickle cell Disease (SCD) is an inherited blood disorder, particularly prevalent in sub-Saharan Africa, that affects over 300,000 newborns worldwide every year. Even though it is a monogenic disease, SCD presents a remarkably clinical heterogeneity. Several studies have demonstrated some polymorphisms that can provide major clinical benefits, producing a mild phenotype. Furthermore, the presence of distinct haplotypes can also influence the phenotype in certain populations, with different clinical manifestations. The aim of this work is to assess the association between polymorphisms in genes previously related to SCD disease severity in Angolan children.

Methods: This study analyzed clinical and biological data collected from 192 Angolan children. Using NGS data, we classify the HBB haplotypes based on four previously described SNPs (rs3834466, rs28440105, rs10128556, and rs968857) and the genotype for the SNPs in HBG2 (rs7482144), BCL11A (rs4671393, rs11886868, rs1427407, rs7557939), HBS1L-MYB (rs66650371) and BGLT3 (rs7924684) genes.

Results: The CAR haplotype was the most frequent HBB haplotype in these population and significant differences were observed in several hematological parameters. The Fetal hemoglobin (HbF) values and the ratio of gamma chains were statistically significant for almost all of the variants studied. We reported the first time an association between rs7924684 in the BGLT3 gene and gamma chains ratio.

Conclusions: The current findings emphasize the importance of personalized medicine would have if applied to SCA patient care, since some of the variants studied might predict the phenotype and the overall response to treatment.

JSCDH-D-21-1038860

HEMOGLOBIN GLYCATION VARIATIONS IN SICKLE CELL DISEASE

Authors: Marcy C. Purnell, Ph.D., APN, FNP-C

Affiliation: *Louisiana State University Health Science Center, School of Nursing*

Background: The current diabetes testing method, hemoglobin A1c or the addition of a sugar to the N-terminal valine of the beta chain, is often unreliable in patients with sickle cell disease and sickle cell trait due to hemoglobin mutations. Recently, a novel potential pathophysiologic mechanism of red cell sickling and dysfunction considering the role of actin in the red cell cytoskeleton and its interaction with serum glucose and serum electrolytes was identified. The objective is to explore alternatives to hemoglobin A1c testing in sickle cell disease and sickle cell trait patients in order to accurately diagnose diabetes and also monitor accurate serum glucose levels that ultimately may contribute to potential red blood cell sickling, dysfunction, membrane failure and crises.

Methods: We conducted a literature review in OVID, PubMed, Google Scholar using key words below.

Results: Hemoglobin A1c levels are often found to be significantly lower in those with sickle cell trait and sickle cell disease, thereby suggesting it to be an inadequate diagnostic tool for diabetes in these populations. Also, there may be a glucose-valine/ATP-driven increased critical concentration of the G-actin +ATP complex along with serum cations that lead to an abnormal polymerization of the critical F-actin protein in the sickle cell red blood cell cytoskeleton membrane complex. This abnormal polymerization of actin could lead to red cell sickling, catastrophic membrane failure and ultimately vaso-occlusive crises.

Conclusions: Increased hemoglobin glycation due to the extra available mutant valines that occur in sickle

cell trait and sickle cell disease patients, may offer a possible explanation for the early destruction of the red blood cells in these patients. Due to the recent discovery that glucose levels may play a role in the cascade to crises, it is important to pursue alternative forms of serum glucose monitoring such as glycated albumin and/or daily blood glucose levels before and after meals. Accurate serum glucose monitoring may not only be critical to the diagnoses and treatment of diabetes in these patient populations, but also may play a role in the transition to crises and in pain management. It is critical that more reliable ways to monitor serum glucose levels in these patients are determined and protocols developed through research.

JSCDH-D-21-1032994

HIBISCUS: A PHASE 2/3 MULTICENTER STUDY OF ORAL PYRUVATE KINASE-R ACTIVATOR FT-4202 IN SCD

Authors: Marilyn J. Telen, MD[1], Jeremie H. Estepp, MD[2], Jo Howard, MB, BChir, MRCP, FRCPath[3], Jason Berlin, MS[4], Irena Webster, MPH, MA[4], Kenneth W. Wood, PhD[4], James Geib, BS[4], Eric Wu, PhD[4], Julie Brevard, MPH[4], Kenneth Ataga, MD[5]

Affiliation: *[1]Department of Medicine, Division of Hematology, Duke University Medical Center, Durham, NC, [2]Departments of Global Pediatric Medicine and Hematology, St. Jude Children's Research Hospital, Memphis, TN, [3]Guy's and St. Thomas' Hospital, London, UK, [4]Forma Therapeutics, Inc., Watertown, MA, Center for Sickle Cell Disease, [5]University of Tennessee Health Science Center, Memphis, TN*

Background: The hallmark of sickle cell disease (SCD) is hemoglobin S (HbS) polymerization upon deoxygenation, resulting in red blood cell (RBC) sickling, hemolysis, and vaso-occlusion. Exacerbating the pathogenesis of SCD, the HbS RBC has increased levels of 2,3-diphosphoglycerate (2,3-DPG), resulting in reduced Hb oxygen affinity (increased p50), and decreased ATP, essential for RBC homeostasis. FT-4202 is an investigational, oral, selective activator of erythrocyte pyruvate kinase (PKR) that increases PKR activity, resulting in decreased 2,3-DPG levels and increased ATP levels in RBCs. Preliminary data from an ongoing phase 1 study (NCT03815695) indicate that FT-4202 is well-tolerated, has no effect on steroidogenesis, and exhibits linear and time-independent pharmacokinetics and associated pharmacodynamic responses (decreased 2,3-DPG and increased ATP). Treatment of patients with SCD for 14 days with once-daily FT-4202 resulted in increased Hb oxygen affinity, reduced RBC sickling, improved RBC deformability, and improved hematologic and hemolytic parameters (Brown, ASH2020_ abstract_#134269). Based on these results a phase 2/3 study, Hibiscus (NCT04624659), has been initiated and is described here.

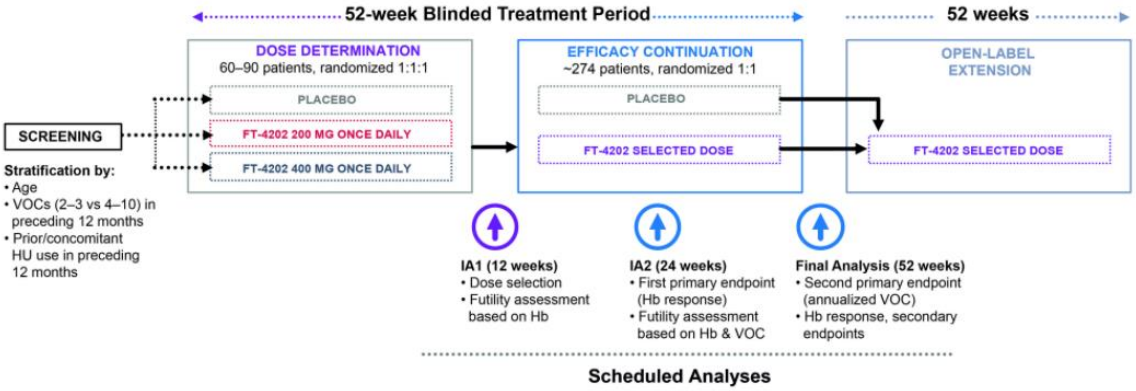
Methods: Hibiscus is a randomized, double-blind, placebo-controlled, phase 2/3 multicenter clinical study designed to investigate the safety and efficacy of FT-4202 in patients with SCD (Figure). Adult and adolescent patients (ages 12–65 years) with SCD (all genotypes and both sexes) will be enrolled in a Dose Determination (DD) group and an Efficacy Continuation (EC) group using an adaptive design. Eligible patients must have had ≥2 vaso-occlusive crises (VOCs) in the past year, baseline Hb ≥5.5 and ≤10 g/dL, and if receiving hydroxyurea (HU), be on a stable dose for the previous 90 days. Patients with >10 VOCs in the past year, hospitalized for sickle cell crisis/other vaso-occlusive event within 14 days of consent, receiving chronic transfusion therapy, significant hepatic/renal dysfunction, history of unstable or deteriorating cardiac or pulmonary disease, or overt stroke within 2 years will be excluded. Co-primary endpoints are Hb response rate at Week 24 (increase from baseline >1 g/dL) measured as the percentage of treated population achieving the endpoint, and annualized VOC rate during the blinded treatment period based on adjudicated VOC review at Week 52. Secondary endpoints include measures of hemolysis, time to first VOC, and the Patient Reported Outcome Measurement Information System fatigue scale. Safety endpoints will also be assessed. Patients will be stratified by number of VOCs in the preceding 12 months, prior/concomitant HU use, and age; randomization will occur in a 1:1:1 ratio to 200 or 400 mg (once-daily) FT-4202, or placebo in the DD group. At interim analysis (IA) 1, the optimal FT-4202 dose will be selected based on safety and Hb response rate at Week 12 in the first 60 patients. EC group patients will be randomized 1:1 to the selected FT-4202 dose or placebo. Once 110 patients randomized to the

selected dose or placebo complete 24-weeks blinded treatment or drop out, IA2 will assess Hb response rate (first primary endpoint). At final analysis (52-weeks blinded treatment) annualized VOC (second primary endpoint), 24-week Hb response rate and all secondary endpoints will be evaluated. Patients may then enter a 52-week open-label extension period at the selected FT-4202 dose. Futility assessments will be conducted (Weeks 12 and 24).

Results: Currently, the Hibiscus study is ongoing and enrolling patients from North America and Europe; planned enrollment: ~344 patients with SCD (DD group, n=60–90; EC group, n~274).

Conclusions: FT-4202 is an investigational, novel disease-modifying therapy that has the potential to become a foundational medication for patients with SCD. Data from the ongoing phase 1 study show that FT-4202 is well tolerated and provide proof of concept. The Hibiscus study is designed to demonstrate efficacy of FT-4202 on the co-primary endpoints of elevation in hemoglobin and reduction in VOC; both of which are areas of unmet medical need in this patient population.

Figure: Study Design



JSCDH-D-21-1040408

HYDROXYUREA TARGETS RAPID PATHWAYS IN RED CELLS TO REDUCE ADHESION IN SICKLE CELL DISEASE

Authors: Urvashi Thongam, BS, Xiufeng Gao, MD, Kimera Harris, Karly Patterson, Jennell White, PhD

Affiliation: *Wayne State University*

Background: Hydroxyurea (HU), the mainstay therapy for sickle cell disease (SCD), was primarily thought to exert therapeutic effects by inducing fetal hemoglobin (HbF) expression, yet prior to significant elevation in HbF levels, clinical symptoms improved suggesting additional mechanisms were involved. Indeed, before any measurable rise in fetal hemoglobin levels, HU reduces adhesion receptor expression and decreases red cell-endothelial interactions. HU has also been shown to modulate cell-to-cell interactions in SCD by altering cell signaling pathways, although mechanisms are not well defined. The objective of this study was to understand the immediate effect of HU on sickle blood cells.

Methods: Whole blood samples were collected from SCD subjects. White blood cells (WBCs) were isolated by density gradient centrifugation; reticulocytes were isolated from packed red blood cells (pRBCs) using dynabead magnetic cell separation technology. Standardized, flow-based adhesion bioassays were utilized to measure adhesion to VCAM-1 in WB, WBC, and reticulocyte samples at baseline and pretreated with varying HU concentrations (50, 200, 400mcM) for 30 minutes.

Results: Adhesion to VCAM-1 was significantly reduced in WB and reticulocyte samples, however HU had no effect on WBC samples.

Conclusions: These data suggest that HU reduces WB adhesion to VCAM-1, independent of WBCs, by targeting immature RBCs through rapid, cell signaling pathways. Future studies are aimed at delineating these mechanisms to reveal novel, therapeutic targets to improve the care for SCD patients.

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IMPULSE OSCILLOMETRY TO EVALUATE LUNG FUNCTION IN YOUNG CHILDREN WITH SICKLE CELL DISEASE

Authors: Nnenna U. Badamosi, MD, MPH[1], Dilys Osei, MD Candidate[1], Tony Ngo, BS[2]

Affiliation: *[1]Medical College of Georgia at Augusta University, [2]Pediatric Comprehensive Sickle Cell Center at Augusta University*

Background: Acute Chest syndrome (ACS) is the leading cause of death in children with SCD between the ages of 2 and 5 years and is the second most common cause for hospitalization behind vaso-occlusive crises. Risk of ACS is higher in children with sickle cell anemia (SCA: Hemoglobin SS and Hemoglobin S beta-zero thalassemia). Obstructive conditions such as asthma and airway hyper-responsiveness are also known risk factors for developing ACS, and are prevalent in older children with SCD. Conversely, repeated episodes of ACS can compromise pulmonary function over time and lead to increased morbidity and mortality.

Despite these risk factors, there are few studies that focus on monitoring airway function in children under 6 years old because of difficulties with effort-dependent tests like spirometry. Impulse oscillometry (IOS) is a non-invasive pulmonary function test that is effort-independent, and has been demonstrated to assess airway function in children as young as 3 years. Impulse oscillometry uses small pressure oscillations during regular breathing to assess resistance (R), reactance (X) and impedance of airways and lung parenchyma.

Our longitudinal study assesses reported asthma symptoms and annual pulmonary function using IOS in our cohort of children with SCA under 6 years old. We sought to demonstrate the feasibility of IOS in long-term monitoring of pulmonary function, and describe baseline pulmonary function in our patients.

Methods: Following Institutional Review Board approval, participants were enrolled in the prospective study during comprehensive sickle cell clinic visits at the Children's Hospital of Georgia in Augusta. Participants were aged 3 – 5.99 years old with known diagnosis of SCA. Parents of enrolled subjects completed the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire to assess underlying asthma symptoms and environmental tobacco smoke exposure. Subjects underwent same day IOS testing, and lung function was assessed using airway resistance at 5Hz and 20Hz (R5, R20), and reactance at 5Hz (X5). Percent predicted values were computed using NHANES (National Health and Nutrition Examination Survey) reference criteria for age, height, gender and ethnicity. Clinical and laboratory data were also obtained from same day appointment or within 6 months of IOS testing to assess disease severity.

Results: Out of 16 consented patients, 15 subjects completed ISAAC questionnaire while 10 successfully performed IOS. One subject had hemoglobin S-beta zero, and the remaining had hemoglobin SS. All participants were African American, and 9 out of 16 were male. Mean age at PFT was 4.7 ± 0.84 years. Thirteen out of 16 subjects were already on Hydroxyurea therapy for their disease with therapy duration ranging from 1 day to 58 months prior to IOS testing. One patient had preceding history of ACS. Two survey respondents reported asthma symptoms (wheezing and/or dry cough at night) in preceding 12 months and 3 reported passive tobacco exposure. One survey respondent reported a prior asthma diagnosis. Of the 10 participants with IOS data, baseline percent-predicted values for R5 and R20 were 112.1 ± 19.0 and 85.1 ± 26.2 respectively. Baseline X5 (%pred) was 89.5 ± 44.9. The mean baseline hemoglobin (g/dL) was 8.77 ± 1.37. The mean fetal hemoglobin percentage was 19.87 ± 9.82,

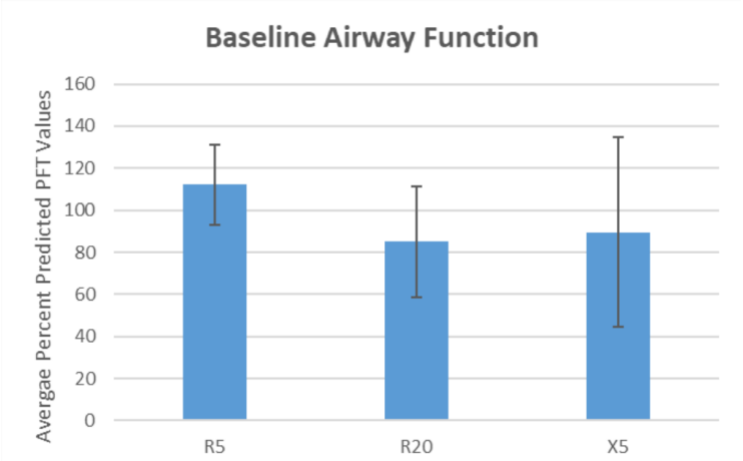
and the mean reticulocyte count percentage was 10.53 ± 5.48.

Conclusions: Our results show normal baseline airway function for majority of our cohort as only 3 subjects had abnormal IOS results. In addition, the mean fetal hemoglobin around 20% suggests mild or well controlled SCA in our young patients. Airway resistance and reactance were used to assess airway function with R5 representing total airway resistance, R20 representing resistance in large airways and the difference between R5 and R20 representing small airway function. Therefore, airway resistance is increased in young children with asthma and obstructive symptoms Low frequency reactance measures the ability of the airway to expand, especially in the distal airways. Therefore, conditions that negatively impact lung elasticity result in abnormal X5 values.

In conclusion, we demonstrated feasibility of impulse oscillometry in monitoring lung function in children with SCA as young as 3 years of age. Further data collection and analysis will improve our understanding of airway function in young SCA patients who may or may not have asthma. Future directions include studying the effects of Hydroxyurea and newer disease-modifying therapies on airway function over time.

Clinical data		
Age in years at PFT (mean ± SD)		4.77 ± 0.84
Male gender		9/16
SS genotype		15/16
Hydroxyurea therapy		13/16
History of ACS		1/16
Laboratory Data (n = 16)	***Mean***	***SD***
total Hb (g/dL)	8.77	1.37
HbF (%)	19.87	9.82
Retic (%)	10.53	5.48
ISAAC questionnaire		
Tobacco exposure		3/15
Asthma symptoms		2/15
Asthma diagnosis		1/15

Patient Characteristics and Clinical Data



Impulse Oscillometry Data

JSCDH-D-21-1039693

INCREASED OPIOID USAGE IN PEDIATRIC SICKLE CELL PATIENTS DURING THE COVID-19 PANDEMIC

Authors: Jennifer Boyd, MD, Deepti Raybagkar, MD, MS

Affiliation: *St. Christopher's Hospital for Children, Philadelphia, PA*

Background: A mainstay of management of sickle cell disease (SCD) is education with patients about known pain "triggers," in an effort to reduce hospitalization, opioid usage, and overall morbidity. The COVID-19 pandemic, with social distancing and the cancellation of in-person school, sports, and other activities that are considered common pain triggers, presents a unique opportunity to evaluate the efficacy of such efforts.

Methods: This was a retrospective chart review of patients with SCD at St. Christopher's Hospital for Children (SCHC), Philadelphia, PA. Participants were selected from the pool of all patients actively receiving care at SCHC as of July, 2020.

The first arm analyzed primarily inpatient data. Inclusion criteria were as follows: patients over age 2 years who had at least 1 hospital encounter, defined as an emergency department (ED) presentation and/or inpatient admission, in March-August 2019 or in the same months in 2020.

The following additional data was collected for patients who had a hospital encounter in both years: number of ED presentations, percent of ED presentations that were due to pain, number of admissions, and total morphine used (in milligrams) during all hospital encounters within the respective year. Additionally, morphine used per patient in the outpatient setting between respective years was totaled via Pennsylvania Drug Monitoring Program (PDMP) filled prescription reporting.

The second part of the study gathered data from 40 additional patients who did not meet the above inpatient inclusion criteria, but required outpatient morphine. Patients were included if they filled at least one prescription within the defined study time frame according to PDMP records. Total morphine filled, in mg, per year was totaled per patient.

Results: For the inpatient arm of the study, a total of 46 patients who met inclusion criteria were identified. Of these, 43% had at least 1 hospital encounter in 2019 and none in 2020. Only 8.6% had at least 1 encounter in 2020 but none in 2019. The remainder, 47%, had encounters in both years. Further analysis of those 22 patients who had encounters in both years was completed. There was a significant increase ($p = 0.05$) in percent of ED presentations that were due to pain crises in 2020 (98.9%) compared with 2019 (84.1%). Also, 81.8% (18/22) of patients required more morphine (in mg) during hospitalizations in 2020, for an average of 163% more. This difference was significant ($p = 0.017$). These same patients also used more morphine as outpatients in 2020 ($p = 0.047$). By ANOVA analysis, there were significant differences between genders: female patients demonstrated a larger increase in ED presentations ($p=.035$) and in hospital admissions ($p=0.10$). In total morphine usage, both males and females had significant increases, and females more than males ($p=.026$). Finally, 65% (26/40) of outpatients in the second arm of the study filled more morphine in 2020 than they did in 2019, for an average increase of 505mg. However, this difference **was not statistically significant ($p = 0.07$).**

Conclusions: Our data supports the idea that trigger avoidance could prevent at least some VOC, hospitalization, and opioid usage. An unexpected result of this study was that those patients who did

require emergency care or inpatient admission in both years used more morphine in 2020. Additionally, other outpatients also used an average of 2.4 times more morphine in 2020, although it was not statistically significant. This study could also further support the role of emotional stress (that is, that which accompanies a global pandemic) and concurrent inflammation in sickle cell pain. More studies are required to elucidate these findings.

JSCDH-D-21-1053446

INTRA-INDIVIDUAL PAIN VARIABILITY AND PHENOTYPES OF PAIN IN SICKLE CELL DISEASE

Authors: Nitya Bakshi, MBBS, MS[1], Scott Gillespie, MS, MSPH[1], Donna McClish, PhD[1], Courtney McCracken, PhD[1], Wally R. Smith, MD [2], Lakshmanan Krishnamurti, MD [2]

Affiliation: [1]*Emory University/Children's Healthcare of Atlanta,* [2]*Virginia Commonwealth University*

Background: Painful vasocclusive episodes are the hallmark of SCD, a chronic multi-system disorder, which affects about 100,000 individuals in the United States and disproportionately impacts minorities and those of lower socioeconomic status. Pain is a major cause of morbidity, and poor health-related quality of life (HRQoL) in SCD, and about one-third of adults with SCD experience daily or near daily pain. There are wide inter-individual differences in the pain experience, and mean pain intensity alone is insufficient to describe pain phenotypes in SCD.

Methods: PiSCES collected daily pain diaries from adults with SCD for a 6-month period. We calculated metrics of intra-individual pain variability and mean pain intensity for 139 participants with < 10% missing daily pain intensity data in the first 28-days of the study. Missing pain intensity scores were imputed by the last observation carry-forward method, for up to 2 missing days. We assessed multiple facets of pain variability: 1) amplitude, measured by the standard deviation, 2) temporal dependency, measured by the first-order autocorrelation, and 3) temporal instability, measured by the mean square of successive differences, and the day-to day probability of acute change in pain. We performed Spearman rank correlations between measures of intra-individual pain variability and outcomes. We then used k-means clustering to identify phenotypes of pain.

Results: We found that pain variability was inversely correlated with HRQoL, except in those with daily or near daily pain. Pain variability was positively correlated with affective coping, catastrophizing, somatic symptom burden, sickle cell stress, healthcare utilization and opioid use.

We found 3 sub-groups or clusters of pain phenotypes in SCD. Cluster 1 included individuals with low mean pain, low pain variability, and lowest proportion of pain days and opioid use. Individuals in Cluster 1 tended to be younger and have the best HRQoL scores, along with lower levels of catastrophizing, stress and use of affective coping strategies. Cluster 1 most consistently differentiated itself from clusters 2 and 3 on subscales of HRQoL and psychological factors. Cluster 2 included individuals with the highest levels of mean pain, highest temporal dependency, and highest proportion of days with pain and opioid use. Cluster 3 included individuals with high levels of mean pain, highest temporal instability, but with lower temporal dependency, proportion of days with pain and opioid use when compared to cluster 2. Differences between cluster 2 and 3 were limited to physical function and social function with cluster 3 having higher median scores as compared to cluster 2 on these subscales, but individuals in cluster 3 were younger than individuals in cluster 2. Psychological characteristics were similar between cluster 2 and 3, but different from cluster 1. The proportion of days with opioid use was different across all 3 clusters, with cluster 2 having the highest proportion of days with opioid use, despite having lower proportion of days with crisis as compared to cluster 3. There was no difference in median number of SCD comorbidities, or proportion of patients with avascular necrosis between the 3 clusters.

Conclusions: We conclude that intra-individual pain variability is associated with patient outcomes and psychological characteristics in SCD, and is useful in delineating phenotypes of pain in SCD.

JSCDH-D-21-1053420

L-GLUTAMINE REDUCES COVID-19 SEVERITY SUGGESTING ADDED BENEFIT IN SICKLE CELL DISEASE

Authors: Philippa Sprintz[1], MD, Aidan Faller[2], Lanetta Jordan[3], Gershwin Blyden, MD[3], Susan Perrine, MD[2]

Affiliation: *[1]Hasbro Children's Hospital, [2]Phoenicia BioScience, Bates College, [3]Foundation for Sickle Cell Disease Research*

Background: Severe acute respiratory syndrome, a leading cause of mortality from SARS-coronavirus-2 (SARS-CoV-2, COVID-19), has pathophysiologic features similar to Acute Chest Syndrome in Sickle Cell Disease (SCD) with inflammation and vascular damage. The Centers for Disease Control designates patients with sickle cell disease as at increased risk for severe COVID-19. Fatalities reported to the COVID-19 SCD registry have occurred in all age ranges and in asymptomatic to severely ill subjects at diagnosis. Readily available safe therapeutics that can be used when a COVID-19 diagnosis is made are needed to prevent and reduce severe disease in high-risk SCD patients.

Methods: Molecular modeling screens for approved therapeutics which bind and inhibit key viral proteins required for cell entry, viral proliferation, viral gene expression, and studies of COVID-19 infected alveolar AT2 cells which undergo rapid cell death were reviewed. Related clinical trials which assessed severe COVID-19 and required ICU care were also reviewed.

Results: Molecular modeling based on altered expression of genes and proteins required for Sars-CoV-2 viral entry identified Vitamin D3, Quercetin (a plant-derived anti-oxidant, anti-inflammatory, and anti-viral agent), as mitigating for severe COVID-19 (Glinsky, Biomedicines, 2020). Quercetin, and Vitamin D3 were projected to interfere with 85% and 70% of critical SARS-CoV-2 proteins respectively. Vitamin D deficiency is common in older adults, patients requiring ICU admission, and in SCD patients. Computational screens of FDA-approved agents directed to spike protein and protease binding targets, and gene expression changes induced by SARS-CoV-2, predict Glutathione and its precursor L-Glutamine as conferring benefit in COVID-19 (Kim, J Translat Med, 2020). Characterization of SARS-Co-V2 infection of AT2 cells demonstrated delayed production of interferons, elevated IL-6, and rapid apoptosis (Kotton et al, 2020). In experimentally induced ARDS, glutamine reduces oxidative lung damage, and IL-6, a cytokine mediator of excessive inflammation, and improves survival in animal models and ICU patients. Pharmaceutical grade L-Glutamine has been shown to reduce acute events in SCD including Acute Chest Syndrome by 63% compared to controls in a Phase 3 trial (Niihara et al, NEJM, 2018).

A controlled clinical trial in 58 patients hospitalized with COVID-19 respiratory disease, with significant hypoxia and CT-confirmed infiltrates, demonstrated fewer ICU admissions (0 vs 13%, p=0.038), and less impaired sequential organ failure assessment (qSOFA score, 0 vs 26%, p = 0.015) in standard care with glutamine-treated subjects compared to controls receiving standard care alone (Cenzig, Clin Nutr Exper, 2021).

Conclusions: Target binding and gene expression computational models predict that Vitamin D, Quercetin, and L-Glutamine should reduce the severity of COVID-19. Characterization of SARS-CoV2 infection of AT2 cells shows similar pathology to ACS and clinical data now show that L-Glutamine reduces severity in hospitalized hypoxic patients with COVID-19 respiratory disease and positive CT scans.

These findings collectively provide a rationale for outpatient implementation of FDA-approved safe therapies to reduce severe COVID-19 disease. The findings strongly suggest that Endari, an FDA-

approved formulation of L-Glutamine specifically for sickle cell disease, should be utilized for newly diagnosed COVID-19 in SCD patients.

JSCDH-D-21-1033018

PATIENT STARTS AND PATIENT AND PROVIDER SATISFACTION WITH THE OXBRYTA® (VOXELOTOR) HUB SERVICE PROGRAM: A RETROSPECTIVE

Authors: Anne Beaubrun, PhD, Rupali Sardesai, MS, Nikhil Bhat, MBA, Rochon Kim, MBA, Irene Agodoa, MD

Affiliation *Global Blood Therapeutics, South San Francisco, CA, USA*

Background: Sickle cell disease (SCD) is a chronic, debilitating disorder that requires lifelong management to mitigate SCD-related complications and reduce the risk of early mortality. Available disease-modifying therapies could potentially reduce the risk of morbidity in this patient population. However, medication initiation and adherence in patients with SCD are impacted by a myriad of factors such as access to care, comorbidities, reimbursement, and patient–provider communication. To provide additional patient support, Global Blood Therapeutics (GBT) implemented a hub service program (HUB) for Oxbryta, GBT Source Solutions®, to offer patient education and support, assist with reimbursement services, and connect patients to a specialty provider. HUB services included, but were not limited to, connecting patients with care coordinators to better understand their insurance benefits, and a nurse support team to answer their questions about their medication. We assessed patient, health care provider (HCP) and practice manager satisfaction with the Oxbryta HUB and report the impact of HUB service enrollment on Oxbryta initiation and adherence in patients with SCD.

Methods: The analysis included patients with SCD aged ≥12 years who were prescribed Oxbryta and enrolled in the HUB from December 2019 to December 2020. To assess patient satisfaction with the HUB, a 35-minute online survey was conducted in Q1 2021 to understand patients' beliefs around SCD treatment, as well as perceptions of the HUB. To assess HCP and practice manager satisfaction with the HUB, a 30-minute online survey was sent directly to participants during Q1 2021. Data were weighted by respondents' self-reported SCD patient load.

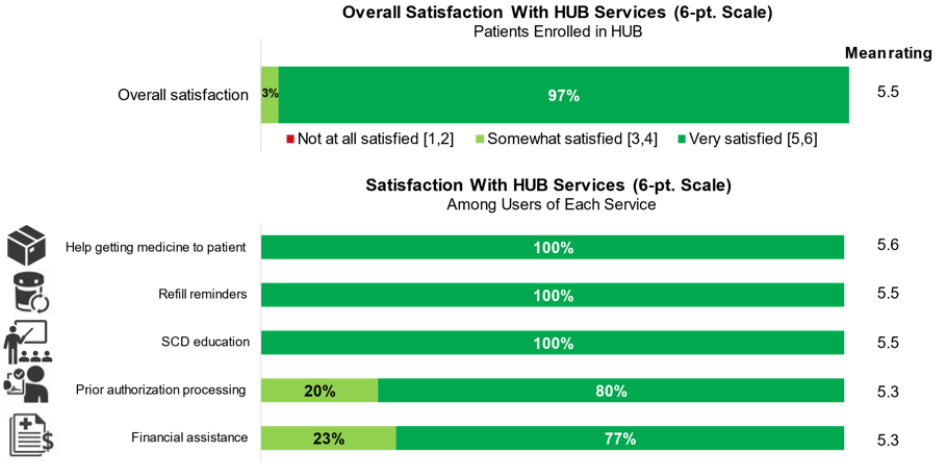
The percentage of patients who initiated Oxbryta after being enrolled in the HUB, as well as patient adherence to treatment was assessed. To assess patient adherence to treatment, the medication-possession ratio (the percentage of available prescriptions filled at 180 days) was reported.

Results: In total, approximately 5000 patients were included in the analysis. Among those who consented, 60% were women, with the majority of patients between the ages of 12 and 34 years. Approximately 40% of HUB patients received Medicaid. Among HUB patient respondents, overall satisfaction with HUB was high across all services with mean satisfaction scores ≥5.3 out of a possible 6 points (Figure 1). Overall satisfaction among practice managers who referred patients to the HUB was high, with a mean satisfaction score of 5.0 out of 6 possible points. Among HCPs who responded to the satisfaction survey, there was a similar proportion of physicians reporting a high overall satisfaction with the HUB. Following enrollment in HUB, a high percentage of patients (76%) initiated Oxbryta treatment and over the first 180 days of therapy, HUB patients had high rates of adherence.

Conclusions: In this real-world, retrospective analysis of enrollment in the Oxbryta HUB (GBT Source Solutions®), a comprehensive program that provides patient access to support and education, overall patient satisfaction with the HUB was high across services used, including financial assistance, help getting medication, prior authorization processing, and refill reminders. Similarly, satisfaction with HUB

services was high among HCPs and practice managers across specialties who referred patients to GBT Source Solutions®. High rates of patient initiation of and adherence to Oxbryta treatment were also observed. Physician reinforcement of the potential advantages of a hub service at the time of prescribing may be a beneficial intervention to advance meaningful treatment outcomes for patients with SCD.

Figure 1. Patient Satisfaction With HUB Services



HUB, hub service program; SCD, sickle cell disease.

JSCDH-D-21-1040239

OUTCOMES OF OSTEONECROSIS OF THE FEMORAL HEAD IN SICKLE CELL DISEASE (SCD)

Authors: Vanessa Charubhumi, MD[1], Eric Fornari, MD[1], Regina Hanstein, PhD[1], Irene Chern[2], Adele Heib[2], Caterina Minniti, MD[1]

Affiliation: [1]*Montefiore Medical Center,* [2]*Albert Einstein School of Medicine*

Background: Osteonecrosis of the femoral head (ONFH) is a common complication of SCD. We set out to describe clinical and radiographic outcomes of SCD patients with ONFH, who were treated with (1) core decompression plus bone marrow aspirate concentrate (CD+BMAC) injection or (2) observation alone.

Methods: 264 hips in 157 SCD patients, 42% female, mean age 26.2 years (range, 5.7-54.3 years) with an ONFH diagnosis between 2006 and 2018 were evaluated. 72.3% hips had HbSS/HBSB0 and 17.9% HBSC/HBSB+. Demographics, surgical parameters, patient self-reported pain and ambulatory status were recorded. Femoral head collapse was assessed on Xrays using the Ficat score system. Average follow-up was 8.22 years for the non-operatively treated patients and 2.98 years for the CD+BMAC patients.

Results: 237 hips (89.8%) were treated non-operatively and 27 hips underwent CD+BMAC by one of 5 providers at an average age of 28 years (range 9.7-52.9 years). All were pre-operatively transfused to a Hb of 10 and 74.1% used Hydroxyurea at time of surgery.

Table1 shows comparison of demographic and surgical parameters between treatment groups. Age at diagnosis, BMI, amount of patients with a symptomatic hip at diagnosis and follow-up were statistically significant different between groups (Wilcoxon rank sum test). 4/27 CD+BMAC (14.8%) and 39/237 observation cases progressed to Total Hip Arthroplasty (THA). Ficat stage progression for all treatment groups is shown in Table2 and was evaluated pre THA or at most recent follow-up. Ficat stage progressed in 25.3% non-operatively treated hips and 11/27 (44%) CD+BMAC cases (pre-op Ficat stage4 excluded).

Cox proportional hazards models were used to examine associations of demographic, surgery and radiographic factors with time to THA. For cases treated with observation alone, female gender (HR 2.065, 95%CI 1.090-3.913, p=0.026), the presence of a musculoskeletal comorbidity (HR 4.3, 95% CI 1.965-9.408, p< 0.001), pre-operative femoral head collapse (HR 19.772, 95%CI 7.718-50.652, p< 0.001) increased the risk for THA.

Patient self-reported pain at most recent follow-up (p=0.433) at most recent follow-up was similar between groups (Table1).

Conclusions: This study aimed to compare outcomes of currently used ONFH treatments in subjects with SCD. In this patient group, we found no evidence that CD+BMAC achieved clinical improvement compared to non-operative treatment.

Table 1

Demographic Parameters N (%) or Mean ±SD	Observation N=234	CD BMAC N=25	P-value
Gender, F	99 (42%)	12 (44%)	*0.838*
Age at Dx (years)	19.0 (15.0, 21.9)	25.1 (18.6, 34.1)	***0.001***
Age at Dx ≤21 years	99 (42%)	20 (74%)	***0.002***
BMI at Diagnosis/Surgery	22.4 (20.0, 26.8)	21.2 (18.2, 27.8)	*0.695*
Ethnicity, self-reported			*0.290*
African American/black	174 (73.4%)	17 (63%)	
Other	4 (1.7%)	1 (3.7%)	
Caucasian	1 (0.4%)	0 (0%)	
Hispanic	48 (20.3%)	6 (22.2%)	
Unknown	10 (4.2%)	3 (11.1%)	
Follow-Up (years)	8.22 (4.3, 11.0)	2.98 (2.2, 3.9)	***<0.001***
Time Dx to Sx (years)	0.61 (0.22, 1.14)	1.59 (0.52, 4.82)	***0.001***
Hip Symptomatic, yes	172 (73%)	23 (92%)	0.050
Femoral head collapse pre-op, yes	73 (31.9%)	11 (40.7%)	0.389
Surgical Parameters			
Hydroxyurea dose at Surgery, mg/kg	20 (16, 25)	22 (22, 27)	***0.031***
EBL (ml)	310 (200, 600)	10 (10, 10)	***<0.001***
Length of stay (days)	5 (3.5, 6.5)	2 (2, 3)	***<0.001***
Transfusion peri-op, yes	17 (46%)	1 (4%)	***<0.001***
Complications			
Progression to THA	39 (16.5%)	4 (14.8%)	*1.000*
Time to THA (years)	1.47 (0.5, 4.0)	0.68 (0.5, 1.6)	*0.448*
Hip Pain at Follow-Up, yes	70 (31%)	6 (23.1%)	*0.502*

Table 2

		Post-op Ficat score, # of cases (%)					
Treatment Group	**Ficat score at Dx**	**I**	**II**	**III**	**IV**	**Pre Ficat score**	**THA**
Non-op	I (7)	1 (14.3%)	5 (71.4%)	1 (14.3%)	0	I (10)	0
	II (123)	1 (0.8%)	97 (78.9%)	9 (7.3%)	16 (13%)	II (141)	5 (3.5%)
	III (11)	0	2 (18.2%)	3 (27.3%)	6 (54.5%)	III (13)	3 (30.8%)
	IV (55)	0	1 (1.8%)	4 (23.5%)	50 (90.9%)	IV (59)	30 (50.8%)
CD+BMAC	**Ficat score at Sx**	**I**	**II**	**III**	**IV**	**Pre Ficat score**	**THA**
	I (1)	0	1 (100%)	0	0	I (1)	0
	II (15)	2 (13.3%)	8 (53.3%)	3 (33.3%)	0	II (15)	0
	III (8)	0	0	3 (37.5%)	5 (62.5%)	III (8)	3 (37.5%)

Comparison of Radiographic Progression of Femoral Head AVN Between Treatment Groups

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PRECLINICAL SAFETY OF HUMAN PLASMA DERIVED HEMOPEXIN FOR THE TREATMENT OF ACUTE VOC IN SCD

Authors: Tanja Ruthsatz, Gerald Hoebarth, Joseph Bain, Thomas Gentinetta, Kirstee Martin, Roslyn Davis, Daniel Schu, Gregory Kato, Eva Herzog

Affiliation: *CSL Behring Innovation GmbH*

Background: Sickle cell disease (SCD) is an inherited, autosomal recessive disorder that leads to hemolytic anemia and vascular disease, with a range of acute and chronic complications driven by self-perpetuating cycle of vaso-occlusion and vaso-occlusive crises (VOCs). CSL889, a human plasma-derived hemopexin, is being developed as a novel pharmacologic therapy to reduce toxic cell-free heme in patients with VOC, with the goal of reducing the duration and severity of acute VOC in adults and children with SCD.

Methods: All studies were conducted under applicable animal welfare standards and regulatory approvals. The in-vivo toxicological program included 2-week repeat-dose tolerability studies in wild-type (C57BL/6) and Townes HbSS sickle cell mice (Hbbtm2(HBG1,HBB*)Tow), a 2 week repeat-dose toxicity study in rats (Sprague Dawley) and a 2 week repeat-dose toxicity study in cynomolgus monkeys (Macaca fascicularis) including cardiovascular safety pharmacology. The latter studies included a treatment free period of 7 days. A single dose safety pharmacology study in rats assessed effects on respiratory parameters. CSL889 was administered intravenously (IV) at dose levels of 50 to 500 mg/kg.

Results: Repeat-dose administration of CSL889 every other day over two weeks was well-tolerated in cynomolgus monkeys and rats. There were no mortalities or adverse findings regarding clinical observations, body weights, ophthalmoscopy, electrocardiography, blood pressure, respiratory rate, clinical chemistry, hematology, coagulation, urine analysis, organ weights, gross pathology or histopathology attributable to treatment with CSL889. Non-adverse and transient effects which returned to baseline levels after the 7-day recovery period included an increase of the beta-globulin serum levels in cynomolgus monkeys, an increase of the alkaline phosphatase (ALP) serum levels which did not clearly follow the dose-response principle in rats, and a small but statistically significant decrease from baseline activated partial thromboplastin time (aPTT). The observed formation of anti-drug antibodies (ADAs) against CSL889 in both species is an expected immune reaction after repeated application of the heterologous human proteins to animals and is not considered predictive for the clinical situation. ADA formation did not have an impact on safety or exposure of the study animals. Safety pharmacology evaluation did not show any deleterious effects of CSL889 on cardiovascular and respiratory functions in cynomolgus monkeys and rats. The NOAEL for rats and cynomolgus monkeys was at least 500 mg/kg under the conditions of the study. Daily IV and subcutaneous (SC) administrations of hemopexin for two weeks to wildtype mice was well tolerated and produced no adverse clinical observations at 160 mg/kg IV and 500 mg/kg SC. While there were no findings after the first dosing occasions, high dose IV animals (500 mg/kg) showed a short-lived, transient clinical reaction, ie reduced mobility and body temperature to the treatment on Day 8. There was no clear evidence of treatment-related changes to hematology or clinical chemistry parameters in any dose group at the end of the dosing period. Daily IV administration of hemopexin for two weeks or six days (500 mg/kg only) to Townes HbSS mice was generally tolerated. Similar to the reaction observed in wildtype mice immunological reactions were observed in some dosing groups after repeat administration, which are assessed as a result of the application of the heterologous human protein.

Conclusions: The toxicological program demonstrated that CSL889 has a favorable safety profile and supports the clinical development of hemopexin for the treatment of acute VOC in sickle cell disease.

JSCDH-D-21-1053281

SICKLE CELL DISEASE AND SOCIAL DETERMINANTS OF HEALTH - A SCOPING REVIEW

Authors: Hamda Khan, MA, Matthew Krull, BS, Jane Hankins, MD, MS, Winfred Wang, MD, Jerlym Porter, PhD, MPH

Affiliation: *St. Jude Children's Research Hospital*

Background: Individuals with sickle cell disease (SCD) experience poor health outcomes, however the extent of the impact of social determinants of health (SDoH) is not clear. Our review aims to elucidate the relationship between SDoH and SCD outcomes and identify gaps in the literature where further research is needed.

Methods: A comprehensive literature review of five electronic databases (PubMed, SCOPUS, CINAHL, PsycINFO and Web of Science) was conducted using Arksey and O'Malley's scoping review framework and checklist for PRISMA-ScR. The search yielded 59 articles meeting eligibility criteria. Findings were organized into five Healthy People 2020 SDoH areas: Education, Economic Stability, Health and Healthcare, Neighborhood and Built Environment, and Social and Community Context.

Results: The evaluated studies demonstrated that parental education, home environment and nutritional status determined cognitive functioning in patients with SCD. Living in poor neighborhoods and decreased access to healthcare resources increased the odds of experiencing more vaso-occlusive events. High utilization of emergency care resources due to frequent pain events increased healthcare expenditure. Climate change, air pollution, and tobacco smoke exposure negatively impacted health outcomes by increasing respiratory problems. Social support and positive family functioning significantly improved self-management and health-related quality of life.

Conclusions: This review found that SDoH, such as limited access to healthcare, neighborhood distress and various other factors, was inconsistently evaluated in the sickle cell population. Improved understanding and recognition of the relationship between SDoH and SCD should result in better health outcomes for patients with SCD.

JSCDH-D-21-1050293

SICKLE CELL DISEASE TRANSFUSION GUIDELINES: FAMILIARITY AMONG INTERNAL MEDICINE PHYSICIANS

Authors: Yating Wang, M.D.[1], Irisha Badu, MD[1]., Yadana Oo, M.D.[1], Lewis Hsu, M.D., PhD[2]

Affiliation: *[1]Weiss Memorial Hospital, [2]University of Illinois at Chicago*

Background: Red cell transfusions remain a mainstay of therapy for patients with sickle cell disease (SCD). However, the indications and identification of transfusion-related adverse events pose significant clinical challenges to the general internist. A knowledge deficit of SCD blood transfusion protocols among internists affect proper management of this subgroup. The ability to identify the indications of transfusion, as well as screen, prevent and manage alloimmunization, delayed hemolytic transfusion reaction and iron overload are hypothesized to improve their outcome. Our aim was to identify, analyze and develop a model to enhance the general physician's knowledge of current national guidelines for blood transfusion in SCD patients in a community hospital setting.

Methods: A questionnaire was created at using a freely available online tool, requiring a time commitment of approximately 2 minutes. This 'pre-intervention' questionnaire (QA1) was sent to the target audience (internal medicine residents and attending physicians) via email along with an invitation to participate in the intervention. A 40 minute oral presentation consisting of 15 minutes of pathophysiology of sickle cell disease followed by 10 minutes of case presentation and 15 minutes of introduction of ASH Guidelines for SCD blood transfusion was conducted with target audience as the intervention. The same questionnaire was sent again to re-assess respondents' knowledge 'post-intervention' (QA2).

Results: There were 31(65% of expected) participants in the oral presentation. They consisted of 8(42.1%) participants of age less than 30 years and 10(52.6%) aged 30 to 40 years. 19(61%) participants responded to QA1, with 1 person not completing it. We received 8 completed responses to QA2. in QA1, 47%(n=19) responses were male. 47% were first year IM residents compared to 26% second years. Average score on QA1 was 36.8%. 39% respondents with previous experience in hematology or SCD related fields scored an average of 47.5% compared to an average score of 29% in 61% who did not (p=0.48). 95% respondents did not have any family or friends with SCD.

In QA2, average score was 75%. Among those residents (n=6) who revealed their identities (for comparison of QA1 and QA2), the average improvement rate is 21.6%. 50% respondents with previous experience in hematology or SCD related fields scored an average of 70% compared to an average score of 80% in 50% who did not (p=0.47).

Conclusions: Physicians who have experience of managing sickle cell disease or related fields are more familiar with SCD blood transfusion, but the prior experience to SCD has not necessarily translated to increase familiarity of SCD transfusion guidelines. Without education, physicians in a community hospital have limited knowledge about current SCD transfusion protocols. This can potentially lead to delay or improper care for SCD patients. An intervention in the form of oral presentation can reduce the knowledge gap and familiarize frontline physicians with modern ASH guidelines leading to better outcomes. Future studies can disseminate this focused training approach to larger numbers of participants at community hospitals.

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THE BURDEN OF SICKLE CELL ANAEMIA IN CENTRAL AFRICA

Authors: TSHILOLO M. Tshilolo[1], BARON D. Ngasia[2], Jean Paul Gonzalez[2]

Affiliation: *[1]CEFA, [2]REDAC network*

Background: To describe the natural history of SCD in Central Africa.

Methods: A descriptive study of SCD based on previous experience in Central African countries. Data base were collected from different countries and analysed with a spss device.

Results: Worldwide, the prevalence of SCD is highest in sub-Saharan Africa. The prevalence of sickle cell gene carriers varies between 5% and 40% of the population, and most children die in early childhood without being diagnosed or because treatment protocols have not been adapted to the local situation. According to a recent Word Bank publication, Sickle cell anemia ranked as the 16th-leading cause of disability in most countries in SubSaharian Africa (SSA); but in Nigeria, SCA was the seventh top driver of disability in 2010. Early identification, control and management of SCD is necessary to prevent childhood deaths.

Late and Under diagnosis of SCA

Newborn screening of SCD has been implemented in most of the subsaharian countries (Nigeria, Ghana, Benin, DRC, Tanzania, Gabon, Cameroon, Angola) as a pilot studies but not really as a systematic national program. Sickle cell management program are mainly located in the urban areas and rarely available in rural areas where live most of the African populations.

Globally, the prevalence of betaS gene in newborns is in Central Africa around 15% (AS) and 1-2% % (SS) with some differences according to the ethnic distribution and the prevalence of malaria (3)

Severe expression

SCD is characterized by a variable phenotype expression depending on genetic and environmental factors. The more severe form seems to be related to people bearing the Bantu's haplotype and living mainly in Central African countries.

Central African SCA patients displayed some specific clinical features: Hand foot syndrome, sepsis and acute anaemia are the early clinical signs; persistent of a large spleen is still observed in 30-40% of patients aged >5yrs. Torrential nose bleeding, tooth decay and hypertrophic tonsillitis are frequent in young patients. Osteomyelitis are severe and often with multiple localization. Malaria is still one of the cause of hospitalization in SCA patients; while clinical evident stroke seems to be less frequent (prevalence< 5%) than what reported in the literature. SCA patients from DRC displayed a permanent inflammatory and under nutrition status and developed high titres of auto antibodies.

Hematologic parameters in SCA patients, in steady state, displayed a mean value of Hb at 7.2 g/dl and reticulocytes at 8.8%; a leucocytosis (14.9 g/L) associated with eosinophilia (7.8%) and monocytosis (14%). Mean value of HbF was around 8%. The recent CADRE study showed that microalbuminuria is significantly more frequent in the SS patients and occurs particularly early in African children.

The blood transfusion rates to 40% and the risk of contamination by viral infections (HIV, VHB and VHC) from 10 -15% to 5-8%. Hydroxyurea is progressively introduced in some of the Central African countries.

Conclusions: Knowledge of the natural history of SCD in SSA countries is one of the objectives pursued by the network REDAC in other to contribute to training and Education for SCD; research and to promote key policies that governments in Africa are able to implement as recommended by the WHO.

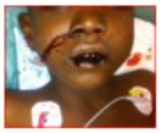
Context in Africa

- **Tropical climate:**
  - malaria endemic,
  - High prevalence of HIV (4-15%)
- **Socio economic conditions:**
  - Poverty and Undernutrition
  - independence since 50 years
  - Very rare Comprehensive SCA programs
- **Homogenous population**
  - Bantu haplotype: > 80%
  - Alpha-thal deletion: 10-40%
  - G6PD deficiency: 20-40%

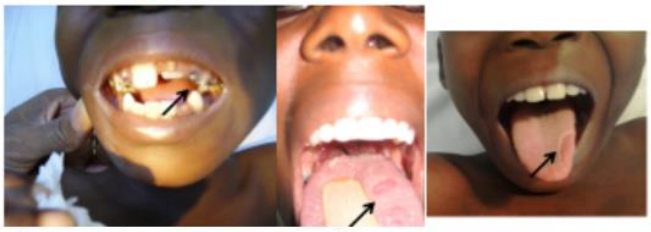
Context of SCD in Central Africa

NTE manifestations

- Torrental Nose bleeding



- Hypertrophic tonsillitis
  Upper air obstruction
- Geographical Glossitis
- Dental abnormalities



NTE specific complications in Congolese SCA Patients

JSCDH-D-21-1039067

UPDATED RESULTS FROM THE HGB-206 STUDY OF LENTIGLOBIN FOR SICKLE CELL DISEASE GENE THERAPY

Authors: Lakshmanan Krishnamurti[1], Alexis A. Thompson[2], Mark C. Walters[3], Janet L. Kwiatkowski[4], Markus Y. Mapara[5], Stacey Rifkin-Zenenberg[6], Banu Aygun[7], Kimberly A. Kasow[8], Manfred Schmidt[9], Mauris Nnamani[10], Alex Miller[10], Meghan Gallagher[10], Xinyan Zhang[10], Dennis Kim[10], Sunita Goyal[10], Julie Kanter[11], John F. Tisdale[12]

Affiliation: *[1]Aflac Cancer and Blood Disorders Center, Department of Pediatrics, Children's Healthcare of Atlanta, Emory University, Atlanta, GA, USA, [2]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA, [3] UCSF Benioff Children's Hospital, Oakland, CA, USA, [4]Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA, [5]Division of Hematology/Oncology, Columbia Center for Translational Immunology, Columbia University Medical Center, New York, NY, USA, [6]Hackensack University Medical Center, Hackensack, NJ, USA, [7]Cohen Children's Medical Center, Queens, NY, USA, [8]University of North Carolina, Chapel Hill, NC, USA, [9]GeneWerk GmbH, Heidelberg, Germany, [10]bluebird bio, Inc., Cambridge, MA, USA, [11]University of Alabama Birmingham, Birmingham, AL, USA, [12]Cellular and Molecular Therapeutics Branch NHLBI/NIDDK, National Institutes of Health, Bethesda, MD, USA*

Background: Sickle Cell Disease (SCD) is a progressive disease caused by a single point mutation in the β-globin gene. Despite lifelong treatment (tx) options, SCD results in painful vaso-occlusive events (VOEs), progressive vasculopathy, and chronic hemolytic anemia, leading to significant morbidity and early mortality. LentiGlobin for SCD (bb1111) gene therapy (GT) utilizes a modified human β-globin gene that produces GT-derived anti-sickling hemoglobin (Hb)AT87Q. The Phase 1/2 HGB-206 study is the largest clinical trial of GT in SCD to date. Beyond the 20 August 2020 data-cut, two Suspected Unexpected Serious Adverse Reactions were reported in HGB-206. One patient from Group A (not reported in these data) who was treated >5 years ago was diagnosed with AML, and based on the results of the recent investigations, this case is unlikely related to the lentiviral vector (BB305). The second case is in a patient from Group C with persistent anemia and is discussed in the Results section, together with Group C efficacy and safety data. As of February 2021, HGB-206 is on clinical hold.

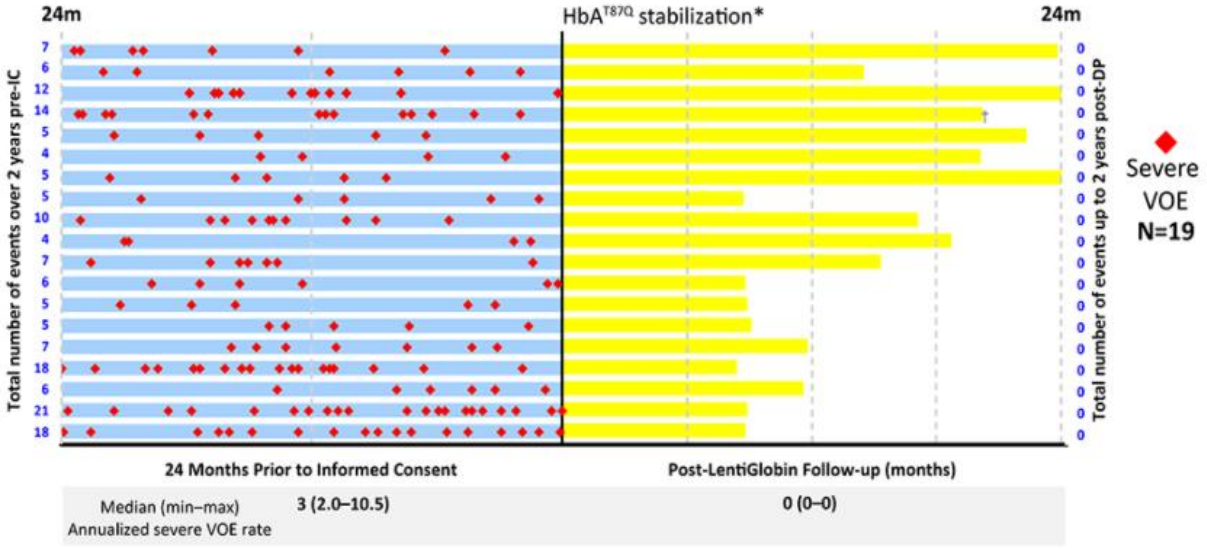
Methods: In 11 centers in the USA, patients (≥12–≤50 yrs) with SCD and recurrent severe VOEs, including acute episodes of pain and acute chest syndrome were enrolled. CD34+ cells were collected by plerixafor mobilization/apheresis and transduced with BB305 lentiviral vector. LentiGlobin was infused after myeloablative busulfan conditioning. Lab evaluations, SCD-related outcomes, pain intensity using Patient Reported Outcomes Measurement Information System (PROMIS)-57, and safety were assessed; data are median (min–max) unless otherwise stated.

Results: As of August 20, 2020, 43 patients (24 [12–38] yrs; male, n=25 [58%]) had initiated cell collection, 32 of whom were treated with LentiGlobin and followed for 13.0 (1.1–30.9) months. Neutrophil and platelet engraftment were achieved at 19.5 (12–35) and 30 (18–136) days, respectively; all patients stopped red blood cell (RBC) transfusions by 90 days post-tx. Near pancellular expression of HbAT87Q was observed ≥6 months post-tx with ~90% of RBCs containing βA-T87Q by 18 months (n=10). At last visit in evaluable patients with ≥6 months follow-up

(n=22), total Hb was 12.0 (9.6–15.1) g/dL; HbAT87Q and HbS contribution to total Hb were 5.6 (2.7–8.9) and 6.1 (4.8–7.8) g/dL, respectively. At last visit in adolescents with ≥6 months follow-up (n=6), median total Hb and HbAT87Q were 13.5 and 6.1 g/dL, respectively. At last visit, lactate dehydrogenase, total bilirubin, and reticulocytes (n=32 for all) approached normalization. In 19 patients with a history of ≥4 severe VOEs and 6 months of follow-up, complete resolution of VOEs was observed after 6 months, with no reports of severe VOEs in the 24 months post-tx compared with an annualized severe VOE rate of 3 (2.0–10.5) in the 24 months prior to informed consent (Fig.). Overall mean PROMIS-57 pain intensity scores decreased from 4.5 at baseline (n=19) to 1.3 at Month 24 (n=4). Tx-emergent serious adverse events (TESAEs) reported in ≥2 patients included abdominal pain, opioid withdrawal syndrome, nausea, and vomiting. All other TESAEs were reported in 1 patient. No SAEs were considered related to LentiGlobin. One patient had a nonserious Grade 2 event of febrile neutropenia considered to be LentiGlobin-related by the investigator. One death, unlikely related to LentiGlobin, occurred >18 months post-tx in a patient with significant baseline SCD-related cardiopulmonary disease. Beyond the August 20, 2020 data cutoff, one patient in Group C had persistent anemia 6 months after transplant; the case is currently being investigated.

Conclusions: LentiGlobin tx resulted in complete resolution of severe VOEs up to 24 months post-tx and decreased patient-reported pain intensity from baseline. There was near pancellular HbAT87Q expression and improved SCD pathophysiology after tx. The safety profile of LentiGlobin tx regimen remains generally consistent with myeloablative single-agent busulfan conditioning and underlying SCD. Abstract previously submitted to the European Haematology Association 2021 meeting.

Figure. Complete resolution of severe VOEs post-LentiGlobin treatment



Protocol severe VOEs are shown; Patients with ≥4 severe VOEs at baseline before IC and with ≥6 months of follow-up post-DP infusion are included. A severe VOE was defined as an event with no medically determined cause other than a vaso-occlusion, requiring a ≥24-hour hospital or ER observation unit visit, or ≥2 visits to a day unit or ER over 72 hours with both visits requiring intravenous treatment for the following: acute episodes of pain, acute chest syndrome, acute hepatic sequestration, and acute splenic sequestration. In the last datacut, one patient had a non-serious VOC at Day 107. This event was recorded as an investigator reported VOE but did not meet the definition of a protocol VOE.

*HbA^{T87Q} expression stabilizes within 6 months; †One death, unlikely related to LentiGlobin, >18 months post treatment in a patient with significant baseline SCD-related cardiopulmonary disease.

DP, drug product; ER, emergency room; IC, informed consent; max, maximum; min, minimum; VOC, vaso-occlusive crisis; VOE, vaso-occlusive event.

TABLE OF AUTHORS