JSCDH

FOUNDATION FOR SICKLE CELL DISEASE RESEARCH
SUPPORTING AND PROMOTING HEMOGLOBINOPATHY RESEARCH

Journal of Sickle Cell Disease and Hemoglobinopathies

A Peer-Reviewed Journal Promoting Science, Clinical Care and Public Health in Sickle Cell Disease and Hemoglobinopathies

October 2018 Issue

Lanetta Bronté, MD, MPH, MSPH
Editor-in-Chief

JSCDH Published online October 19, 2018. ISSN: 2330-1473 DOI 10.14223

TABLE OF CONTENTS

JSCDH-D-18-00079 : **MICROALBUMINURIA IN CHILDREN WITH SICKLE CELL DISEASE: DEVELOPING CLINICAL GUIDELINES FOR MONITORING AND REFERRAL**

Authors: 1 Barbara Speller-Brown, DNP, CPNP, 2 Claire Anderson, MD, 1 Shamir Tuchman, MD, 1 Kirtida Misty, MD, 1 Wang Yunfei, PHD, 1 Amy Frantz, CPNP, 1 Josh Coons, MS, Deepika Darbari, MD,

Affiliations: 1Children's National Health System; 2 Great North Children's Hospital New Castle Upon Tyne, UK

ABSTRACT

Background Sickle cell disease (SCD) is an inherited hemolytic anemia affecting millions worldwide. Up to one third of adults with SCD develop chronic kidney disease from intravascular sickling in the hypertonic, hypoxic and acidic environment of the renal medulla with resulting interstitial ischemia and fibrosis leading to hyperfiltration renal injury. Intravascular sickling of red cells may begin in childhood, predisposing to hyperfiltration renal injury, which manifests as microalbuminuria progressing to proteinuria, both of which are known predictors of progression to end-stage renal disease. The purpose of this study was to determine the prevalence of microalbuminuria and proteinuria and its correlates in a pediatric population with SCD.

METHODS

We reviewed 205 clinical records of patients with SCD ages 3 to 21 years. Random urinalysis, urine microalbumin to creatinine ratios, and protein to creatinine ratios were obtained. Clinical information including height, weight, blood pressure (BP) measurement, complete blood and reticulocyte count values, transcranial Doppler (TCD) velocities and current treatments including hydroxyurea or blood transfusions were extracted from medical records. Microalbuminuria was defined as a random urine microalbumin to creatinine ratio (ACR) of 30-300 mg/g creatinine; proteinuria as ACR >300 mg/g creatinine. Proteinuria and hematuria were reported as 1+ to 4+ on dipstick. Data was analyzed to determine the frequency and correlates of microalbuminuria and proteinuria.

RESULTS

Two hundred and five patient records were reviewed. Gender was evenly distributed (102 respectively). One patient was excluded, considered to be an outlier with a ratio >300, to avoid skewing the data. Age ranged from 2.9 to 21.9 years (Mean 11.9). One hundred fifty-four patients had Hb SS disease, 41 Hb SC and 9 Sickle Beta Plus Thalassemia. Thirty-one patients (15.2%) had microalbuminuria and 173 (84.8%) did not. Proteinuria, hematuria, age, height, weight and systolic blood pressure were significantly associated with microalbuminuria with age as the strongest predictor.

CONCLUSION

Renal injury in SCD starts in childhood, and microalbuminuria is an early marker. Age was the greatest predictor of microalbuminuria followed by elevated systolic BP. We propose all children with SCD should be screened by annual urinalysis as well as by careful BP monitoring at each clinic visit for early identification of children at risk for renal injury due to SCD.

JSCDH-D-18-00078 : COMPARISON OF IMPULSE OSCILLOMETRY WITH SPIROMETRY TO ASSESS LUNG FUNCTION IN CHILDREN WITH SICKLE CELL DISEASE (SCD)

Authors: 1Nnenna Ukachi Badamosi, 2Elizabeth K Fiorino, MD, 3Martin Lesser, PhD, 3Karalyn Pappas, 1Abena Appiah-Kubi, MD, MPH, 1Donna Brower, MSN, CPNP, 1Maria Teresa Santiago, MD, 1Banu Aygun, MD,

Affiliations: 1Augusta University; 2Pediatric Pulmonology at Cohen Children's Medical Center, New Hyde Park, NY;Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; 3Feinstein Institute of Medical Research, Manhasset, NY

INTRODUCTION

Although spirometry is a validated pulmonary function test (PFT) for assessment of airway function in older children and adults, it is not consistently reliable in children less than 6 years of age. Impulse oscillometry (IOS), a technique to evaluate airway function via assessment of airway resistance, has been validated for use in children as young as 3 years, but has not been used widely in children with SCD. We sought to examine the correlation between spirometry and oscillometry in assessment of airway obstruction and bronchodilator response in children with SCD > 6 years old, in order to assess its utility in our patient population.

METHODS

After IRB approval, this prospective study was offered to all eligible patients in our sickle cell clinic who fulfilled age criteria and were due for a clinical PFT study. Clinical and laboratory data on the participants were collected from medical records. Symptoms of asthma and airway hyper-responsiveness were assessed using the modified ISAAC questionnaire prior to lung function testing. Airway function was concurrently assessed pre-and post-bronchodilator using oscillometry (area of reactance, AX; airway resistance at 5Hz, R5) and spirometry (forced expiratory volume in 1 second, FEV1; forced mid-expiratory flow, FEF25-75).

A Pearson's test was run to analyze correlation between percent change from baseline for all variables (AX, R5, FEV1 and FEF25-75). McNemar's exact test was used to compare the proportion of improved patients for AX, R5, and FEV1, FEF25-75. All statistical tests were performed at 5% significance.

RESULTS

Twenty-three (23) out of 31 consented participants completed oscillometry and spirometry successfully. Twenty (20) of 23 participants were African American and 16/23 were male. Age range was 7.3 - 14.7 years at time of study and SCD genotypes included HbSS (16/23), HbSC (3/23), HbSβ+ thalassemia (2/23) and HbSβ° thalassemia (2/23). Of the 22 questionnaire respondents, 10 described history of asthma symptoms but only 4/22 reported experiencing symptoms in the preceding 12 months.

We correlated percent change from baseline between FEV1 vs. AX ($r2 = -0.15$, $p = 0.49$) and FEV1 vs R5 ($r2 = -0.48$, $p = 0.02$), as well as between FEF25-75 vs. AX ($r2 = -0.24$, $p = 0.28$) and FEF25-75 vs. R5 ($r2 = -0.54$, $p = 0.008$). We then compared the percentage of patients with improved bronchodilator response in FEV1 vs. AX (21.74 vs 65.22%; $p = 0.0063$) and FEV1 vs. R5 (21.74 vs 56.52%; $p = 0.02$) as well as FEF25-75 vs. AX (39.13 vs. 65.22%; $p = 0.11$) and FEF 25-75 vs. R5 (39.13 vs. 56.52%; $p = 0.29$)

CONCLUSION

Our findings suggest that airway function as denoted by percent changes in FEV1 and FEF25-75 (spirometry) better correlate with R5 (oscillometry) than AX and that percent change in R5 can serve as a good measure of airway function in children with SCD who are unable to perform spirometry. In addition, a higher proportion of SCD patients showed improved bronchodilator response in oscillometry (AX, R5) when compared to spirometry (FEV1 , FEF25-75), suggesting that impulse oscillometry may be more sensitive in detecting bronchodilator responsiveness in children with SCD when compared to spirometry,

even in children who do not report symptoms of asthma or airway hyper-responsiveness.

JSCDH-D-18-00077: STRATEGIES TO GUIDE HYDROXYUREA ADHERENCE AMONG PATIENTS WITH SICKLE CELL DISEASE: A SYSTEMATIC REVIEW

Authors: 1Lori L. Vick, PhD, RN, 2Maryellen Potts, PhD, 1Megan Jaskowiak, PhD, 3Robert Gibson, Ph.D.

Affiliations: 1Bradley University, 2University of Kansas, 3Augusta University

BACKGROUND

Hydroxyurea/hydroxycarbamide (HU/HC) successfully treats persons with sickle cell disease (SCD), but treatment success requires medication adherence (MA). This systematic review evaluates studies that facilitate adherence as a process and outcome. HU/HC adherence improves health outcomes, reduces disease burden, and decreases healthcare costs. PICO question: In persons with sickle cell disease, what adherence strategies work best to support consistent hydroxyurea utilization?

METHODS

A systematic search of 7 databases (CINAHL, Cochrane, EMBASE, Health Source, PsycARTICLES, PsycINFO, PubMed) was conducted using PRISMA guidelines. Inclusion criteria were English language, human subjects, persons with sickle cell disease, prescription or administration of hydroxyurea (HU)/hydroxycarbamide (HC), and containing references to HU/HC, adherence, adherence interventions, or nonadherence. Relevant studies were retained for full article review and subsequent data extraction. Screening of full-text articles was conducted.

RESULTS

Six studies met inclusion criteria out of 496 reviewed. The total sample across studies consisted of 180 participants. Study designs included 2 randomized controlled trials, 1 non-randomized controlled trial, and 3 cohort studies. Each intervention involved technology. Three studies used text messaging. Two studies used an electronic pill bottle cap to track pill count. Five studies engaged participants in responses to technology. One study used educational materials and personal support for MA and one study used clinic time to meet with participants and families. Adherence was measured by Morisky Medication Adherence Scale, recorded clinic visits, diaries, biomarkers, and lab results. Acceptability and satisfaction of adherence strategy was measured by questionnaires and interviews.

SIGNIFICANCE

Three gaps were found: (1) scant primary research in MA to HU/HC in patients with SCD is being conducted; (2) this research does not typically incorporate a patient-centered definition of adherence, nor the means to measure it; (3) tested interventions do not incorporate theoretical models that include self-management, family, community dynamics, and behavior change.

CONCLUSION

Studies that go beyond monitoring HU/HC medication usage are necessary to explore the efficacy of MA interventions that are grounded in behavioral theories to support persons with SCD achieve better health outcomes.

JSCDH-D-18-00065: IMPROVING ACCESS TO CARE FOR ADULTS WITH SICKLE CELL DISEASE IN LOS ANGELES COUNTY

Authors: Susan Claster, MD[1], Ellen Rothman[2*], Mary Brown[3*], Judith Baker, DrPH, MHSA[4*] and Diane J. Nugent, MD[1]

Affiliations: [1]Center for Inherited Blood Disorders, Orange, CA; [2]MLK Jr Outpatient Center, Los Angeles County Department of Health Services, Los Angeles, CA; [3]Sickle Cell Foundation of California, Ontario, CA; [4]The Center for Comprehensive Care & Diagnosis of Inherited Blood Disorders and University of California Los Angeles, Orange, CA

INTRODUCTION

In 2005 the life expectancy for adults with sickle cell disease (SCD) in Los Angeles (LA) county was 35-38 years (Powars 2005). In 2009 the only comprehensive adult sickle cell program in LA outside the Kaiser system closed. The California Department of Public Health found that 51% of the adults in CA with SCD live in LA county (Paulukonis 2014). The majority of those adults live in South LA. The dearth of programs for adults drives them to seek recurrent care in emergency departments. Recognizing this as a county-wide public health issue, the LA Department of Health partnered with the Pacific Sickle Cell Regional Collaborative (PSCRC) in 2015 to establish an advanced practice medical home at the Martin Luther King Jr. Outpatient Center.

METHODS

The clinic opened August 2016. The staff includes a hematologist with expertise in SCD, a primary care provider, a nurse educator, an MSW, and two community health workers funded by the Sickle Cell Foundation . In the first 18 months we have cared for 33 patients.

RESULTS

This first cohort of patients is notable for health complications due to lack of coordinated, preventive services as measured by: outpatient visits in the 12 months prior to coming to MLK, immunizations, iron overload, and use of Hydroxyurea (HU) (Table). Almost 40 % percent of the patients had no care other than ED or inpatient care for the 12 months preceding their first visit to our clinic. All of the patients were missing one or more adult immunizations. Five patients were severely iron overloaded due to multiple transfusions as inpatients with no hematology follow up to address chelation issues. Forty two percent of the patients(14 patients) seen were eligible for HU but were not on the drug. Eighteen percent (6 patients) were on the drug but were noncompliant or poorly managed with episodes of neutropenia.

CONCLUSION

The creation of an advanced practice medical home for adults with SCD in Los Angeles demonstrates a successful regional approach that engages medicine, public health, and community based organization leaders to build SCD clinical services in less than a year. This safety net clinic now provides team based primary and specialty care to adults whose only option previously was an emergency room. Our statistics reinforce the need for better access to care for adults with SCD.

MLK Clinic 8/16-2/18

Genotype	N	No care past >12 months	Needs immunizations	Severe iron overload	No HU but eligible
SS	21	9	18	4	13
SC	7	2	7	0	0
SB Thal	5	2	5	1	1
TOTALS	**30**	**13**	**30**	**5**	**14**
%	100	**39**	**100**	**15**	**42**

28/30 patients are from the South LA/Long Beach area. All patients have Medicaid and /or Medicare insurance

JSCDH-D-18-00062: IW-1701, A SOLUBLE GUANYLATE CYCLASE STIMULATOR, ATTENUATES INCREASES OF BIOMARKERS OF INTRAVASCULAR INFLAMMATION AND SUPPRESSES LEUKOCYTE-ENDOTHELIAL INTERACTIONS IN TUMOR NECROSIS FACTOR ALPHA (TNFA)-TREATED MICE

Authors: Boris Tchernychev,[1] Susanne Feil,[2] Peter Germano,[1] William Warren,[1] Elisabeth Lonie,[1] Robert Feil,[2] G. Todd Milne,[1] John Hadcock,[1] Yueh-Tyng Chien,[1] Mark G. Currie,[1] Regina Graul[1]

Affiliations: 1. Ironwood Pharmaceuticals Inc., Cambridge, MA, USA; 2. University of Tübingen, Tübingen, Germany

BACKGROUND

In response to nitric oxide (NO), soluble guanylate cyclase (sGC), a heme-containing signaling enzyme, catalyzes the formation of cyclic guanosine 3',5'-monophosphate (cGMP), a second messenger that modulates inflammation and other physiological processes. Treatment with NO donors or inhibitors of cGMP-selective phosphodiesterase 9 (PDE9) attenuates TNFα-induced intravascular inflammation in C57BL/6 and sickle-cell mice. Hydroxyurea (HU), standard care for sickle-cell disease, augments the anti-inflammatory effect of PDE9 inhibitors and may exert anti-inflammatory effects as an NO donor. IW-1701 is an sGC stimulator, a small molecule drug that enhances NO-dependent activity of sGC.

METHODS

We evaluated IW-1701 in the absence/presence of HU on biomarkers of intravascular inflammation, leukocyte-endothelial cell interactions (intravital microscopy), and neutrophil trafficking (peritoneal recruitment model) in C57BL/6 mice.

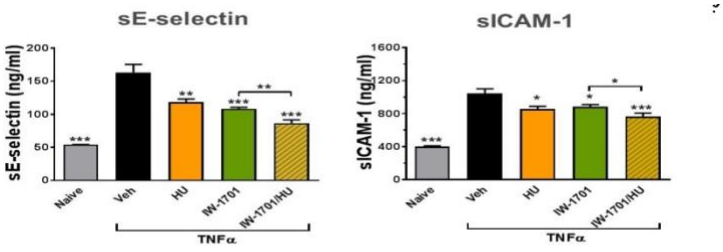
RESULTS

Treatment with TNFα (50 ng/mouse, ip) increased plasma biomarkers of endothelial cell activation (sP-selectin, sE-selectin, sICAM-1) and leukocyte activation (MIP-2, sL-selectin). Pretreatment with IW-1701 (10 mg/kg, po) reduced TNFα-induced increases in plasma sP-selectin, sE-selectin, and sICAM-1 by 31%, 37%, and 34% and MIP-2 and sL-selectin by 81% and 58%, respectively. Co-treatment with HU augmented the effects of IW-1701 on plasma sE-selectin and sICAM-1 (Figure). TNFα decreased leukocyte velocity in venules (from 26.6±3.1 to 5.5±0.7 µm/sec) and leukocyte rolling flux (from 43.3±7.1 to 16.1±2.7 cells/min). Pretreatment with IW-1701 (10 mg/kg) increased leukocyte velocity (10.3±1.1 µm/sec) and rolling flux (24.1±2.3 cells/min); HU (100 mg/kg, po) also increased leukocyte velocity (15.5±1.7 µm/sec) and rolling flux (50.2±5.9 cells/min), while co-administration of IW-1701 with HU further increased leukocyte velocity (19.7±1.9 µm/sec) and leukocyte rolling flux (64.5±5.5 cells/min). Intraperitoneal injection of TNFα induced accumulation of Gr.1-positive neutrophils in the peritoneal cavity ($4\pm0.4\times10^5$ PMNs/peritoneal lavage). Trafficking of neutrophils was attenuated by HU ($2.7\pm0.5\times10^5$ PMNs) and co-administration of HU with IW-1701 further decreased peritoneal neutrophil extravasation ($1.4\pm0.3\times10^5$ PMNs).

CONCLUSIONS

IW-1701 attenuated increases in biomarkers of intravascular inflammation, suppressed leukocyte-endothelial cell interactions, and augmented the effect of HU on neutrophil trafficking. This study supports further evaluation of IW-1701 to reduce complications of intravascular inflammation such as painful vaso-occlusive crisis in patients with sickle-cell disease.

.



Attenuation effect of IW-1701 on E-selectin and ICAM-1, alone and in combination with HU

JSCDH-D-18-00051: IMPLEMENTATION OF A EUROPEAN COHORT TO FOLLOW SICKLE CELL CHILDREN TREATED WITH HYDROXYUREA

Authors & Affiliations: Oevermann L (Berlin, Ger), Brousse V (Paris ,Fr), Benkerrou M (Paris, Fr), Belloy M (Aulnay ss Bois, Fr), Pondarré C (Créteil, Fr), Clouzeau J (St Laurent Du Maroni, Guyana), Steschenko D (Nancy, Fr), Armari-Alla C (Grenoble, Fr), Elana G (Le Lamentin, Martinique), De Montalembert M (Paris, Fr) a*nd all « pediatric investigators » of ESCORT HU**

BACKGROUND

Hydroxyurea (HU) is a fetal hemoglobin inducer authorized for the prevention of recurrent vaso-occlusive crises in adults and children older than 2 years with sickle-cell disease (SCD) in Europe since June 2007, and in the US since 1998 (adults) and 2017 (children).

METHODS

ESCORT-HU (European Sickle Cell Disease Cohort – Hydroxyurea) is a multicenter, prospective, non-interventional study, implemented in Europe to collect more information about the safety profile of HU and morbi-mortality in SCD patients treated with SIKLOS®. The study responds to a request from the EMA (European Medicines Agency) and has been approved by the Ethical committee of Necker Enfants Malades Hospital (Paris, France). The study is ongoing and involves the largest number of patients with SCD treated with SIKLOS® so far. Primary endpoints of ESCORT-HU are the frequency of adverse events, and possible consequent changes of HU treatment. Secondary endpoints evaluate morbi-mortality of the disease although in the absence of a control group.

RESULTS

From January 2009 to June 2017, 1829 patients (1012 females, 817 males) were enrolled from 4 European countries in the study. Among them, 804 patients (43.9%) were younger than 18 years old (389 females, 415 males) at the initiation of SIKLOS®. Demographic data are reported in table 1.

Among children patients, 367 patients (45.6%) experienced 1084 adverse events (AE). As expected in SCD, the most frequently reported AE were infections (392 (36.2%) in 228 patients) and blood disorders including anemia (14.4%). 180 AE of the total of AE, in 97 patients (12.1%) were reported as related to HU.

The most frequent AE related to HU were blood disorders (n=132, 9.1%) such as neutropenia or thrombocytopenia. In all cases, these episodes of cytopenias rapidly resolved with a transitory discontinuation of HU. The second most frequent HU-related group of AEs were skin and subcutaneous tissue disorders (n=28, 3.0%) mostly cutaneous dryness and skin reactions. Most of these events were ongoing or stabilized despite the decrease of HU dose. No secondary cancer has been reported (Table 2).

CONCLUSIONS

The prospective ESCORT-HU cohort study has been implemented to increase the knowledge on SCD in children and the tolerance of HU in this population. The use of HU in pediatric patients is relatively new in non-clinical trial setting. ESCORT-HU may also ensure that the safety profile of HU in SCA is similar to the one reported in adults with SCD. It could identify rare adverse events and it has the ambition to better understand the impact of HU on SCD in real life.

Table 1: Characteristics at the baseline of pediatric population

Number of children patients		804
Number of Females/Males		389/415
Median age (years) [range]		9 [2-17.9]
Genotype	SS	720 (91.6%)
	SC	11 (1.4%)
	Sβ0	31 (3.9%)
	Sβ+	24 (3.1%)
	Other (including missing and unknown data)	18 (2.2%)
Initial daily mean dose (mg/kg/d)		17.2 ±4
Number of patients with HU treatment before enrollment in ESCORT-HU		288 (35.8%)

Table 1 : Most frequent AEs reported in pediatric population in ESCORT HU

	Adverse events			**Adverse events related to HU**		
	NAE	**n**	**%**	**NAE**	**n**	**%**
At least one adverse event	1084	367	45.6	180	97	12.1
Infections	392	228	28.4	1	1	0.1
Blood and lymphatic system disorders	211	116	14.4	132	73	9.1
Skin and subcutaneous tissue disorders	74	53	6.6	28	24	3.0
Nervous system disorders	64	54	6.7	5	4	0.5
Gastrointestinal disorders	86	69	8.6	8	8	1.0
General disorders	72	60	7.5	2	2	0.2
Metabolic and nutrition disorders	53	45	5.6	1	1	0.1
Other Not SCD-related events	22	22	2.7	0	0	0

**And all « pediatric investigators » of ESCORT HU : Arnaud C (Créteil, Fr), Benemou M (Gonesse, Fr), Castex Mp (Toulouse, Fr), , Colombatti R (Padova, It), Divialle-Doumdo L (Pointe à Pitre, Guadeloupe), Dumesnil de Maricour C (Rouen, Fr), Elenga N (Cayenne, Guyane), Garnier N (Lyon, Fr), Grosse R (Hamburg, Ger), Kamden A (Créteil, Fr), Kordes U (Hamburg, Ger), Lesprit E (Trousseau, Fr), Malric A (Saint Denis, Fr), Merlin E (Clermont-Ferrand, Fr), Niekrens C (Delmenhorst, Ger), Odievre Mh (Trousseau, Fr), Paillard C (Strasbourg, Fr), Petras M (Pointe à Pitre, Guadeloupe), Piguet C (Limoges, Fr), Pluchart C (Reims, Fr) Potthoff C (Dusseldorf, Ger), Runel C (Bordeaux, Fr), Sibille G (Basse-Terre, Guadeloupe), Wlodarski M (Freiburg, Ger), Steschenko D (Nancy, Fr), Thuret I (Marseille, Fr), Toutain F (Rennes, Fr), Vantilcke V (St Laurent Du Maroni, Guyana),*

TABLE OF AUTHORS