Revolutionizing Sickle Cell Disease Care in the United States and Abroad: Program

Abstracts in this session examine new approaches to improving outcomes for patients with sickle cell disease, including those in developing countries where outcomes are especially poor. While we know the exact genetic cause of sickle cell disease, there remains a significant lack of effective treatment options and no widely available cure.

Kenneth I. Ataga, et al.

1 SUSTAIN: A Multicenter, Randomized, Placebo-Controlled, Double-Blind, 12-Month Study to Assess Safety and Efficacy of SelG1 with or without Hydroxyurea Therapy in Sickle Cell Disease Patients with Sickle Cell-Related Pain Crises

NEJM - On-line First: K.I. Ataga and Others: Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease

Conclusion: The P-selectin inhibitor SelG1 significantly reduced SCPC and appeared to be safe and well tolerated. Significant improvements were also achieved for several secondary endpoints including increases in times to first and second SCPC. Chronic inhibition of P-selectin with once a month IV dosing of SelG1 represents a novel and potentially new disease-modifying, prophylactic treatment option for patients with SCD. clinicaltrials.gov: NCT01895361

ASH Press Release: In a multicenter clinical trial, the novel targeted drug SelG1 reduced the frequency of pain crises by nearly half compared with a placebo in adolescents and adults with SCD. These results suggest that SelG1 may offer another treatment option for patients with SCD who cannot tolerate or are reluctant to take hydroxyurea — currently the only U.S. Food and Drug Administration (FDA)–approved treatment for complications of SCD — or those for whom hydroxyurea is ineffective.

While normal red blood cells are flexible and can easily move through blood vessels, sickled cells are prone to sticking together and to other blood cells and to the lining of blood vessels, which obstructs blood flow, interrupts oxygen delivery to the body's tissues, and causes severe pain. These painful episodes occur

unpredictably and often require hospitalization. SelG1 is an experimental drug that blocks the action of a protein called P-selectin, which preclinical studies have identified as a prime culprit in the cell stickiness that leads to blood-vessel obstruction.

The SUSTAIN trial involved 198 SCD patients ages 16–65 who had experienced at least two and as many as 10 pain crises during the previous year. Patients were randomly assigned to receive 5 mg/kg or 2.5 mg/kg of SelG1 or a placebo intravenously once a month, after an initial loading dose. Some patients in the trial were also receiving hydroxyurea. After one year, the median annual rate of pain crises was reduced by 47 percent in patients treated with 5 mg/kg of SelG1 compared with those in the placebo group and by 33 percent in patients treated with 2.5 mg/kg of the drug. In addition, the median times to the first and second pain crises were more than 2-fold longer in patients treated with 5 mg/kg of SelG1 compared with placebo.

“Patients who received the highest dose of SelG1 had a significant and clinically meaningful reduction in pain crises,” said lead study author Kenneth I. Ataga, MBBS, of the University of North Carolina at Chapel Hill. “Although some side effects were reported, overall the drug seemed to be very well tolerated. I believe it will make a significant difference in patients’ lives.”

The SUSTAIN trial was not designed to determine whether treatment with SelG1 extends patients’ lives, Dr. Ataga said. Long-term follow-up studies will be needed to establish whether the drug affects survival. Additional studies will also be needed to evaluate the drug in younger children with SCD. SelG1 is not currently approved by the FDA.

Funding for this study was provided by a National Heart, Lung, and Blood Institute Small Business Innovation Research award to Selexys Pharmaceuticals.

Kenneth I. Ataga, MD, University of North Carolina at Chapel Hill, will present this study during the Plenary Scientific Session on Sunday, December 4, 2016, at 2:00 p.m. in Hall AB of the San Diego Convention Center. The study will be simultaneously published in the New England Journal of Medicine *at the time of the press briefing presentation.*

Webcast:

Najibah Aliyu Galadanci, et al.

122 Feasibility Trial for Primary Stroke Prevention in Children with Sickle Cell Anemia in Nigeria (SPIN Trial)

Conclusions: In Nigeria, participants in SPIN Trial with elevated TCD measurements treated with moderate dose of hydroxyurea, showed high rates of successful recruitment, retention and adherence rates to trial medication. Importantly hydroxyurea therapy did not reveal any evidence of excessive toxicity when compared to those not treated with hydroxyurea. Our results provide strong preliminary evidence supporting the current multi-center randomized controlled trial comparing hydroxyurea therapy (20 mg/kg/day vs 10 mg/kg/day) for preventing primary strokes in children with SCA living in Nigeria (1R01NS094041-01;clinical trials.gov NCT 02560935).

ASH Press Release: Results of the first National Institutes of Health–funded study of sickle cell disease (SCD) to be conducted in Africa suggest that a moderate dose of the drug hydroxyurea is safe and may reduce the risk of stroke in children with SCD. These preliminary findings have helped pave the way to a Phase III multicenter randomized trial that is now underway to test hydroxyurea for stroke prevention in a larger population of African children with SCD.

Children with sickle cell anemia (SCA), the most common form of SCD, have a risk of stroke that is more than 300 times greater than that of healthy children.[1] In high-income countries such as the United States, regular blood-transfusion therapy has dramatically reduced this risk. By contrast, in low-resource countries such as Nigeria — home to nearly half of the 300,000 children worldwide born with SCD each year —blood-transfusion therapy is either unsafe, too costly for most patients and families to afford, or both. This feasibility trial was conducted to determine whether hydroxyurea, an oral drug used for more than 30 years to treat complications of SCA, is a safe and acceptable alternate treatment to reduce stroke risk among Nigerian children with SCA.

Twenty-five children with SCA ages 5 to 12 who were at high risk for stroke received a once-daily dose of 20 mg/kg of hydroxyurea. They were compared with 210 children in the same age group who had SCA but were not at elevated risk for stroke. After a median of two years of follow-up, patients treated with hydroxyurea were hospitalized at a rate of 35.1 per 100 patient-years, compared with 48.0 per 100 patient-years for the comparison group. No strokes occurred in the treatment group; one stroke occurred in the comparison group. One patient who had been in the treatment group died of pre-existing kidney failure unrelated to hydroxyurea therapy after being withdrawn from the study; eight patients in the comparison group died.

“In this feasibility trial, we have shown that a moderate dose of hydroxyurea is an acceptable option for primary stroke prevention when blood transfusion therapy is either not readily available or accepted,” said lead study author Najibah A. Galadanci, MBBS, MPH, of Bayero University in Kano, Nigeria. “These results provide strong preliminary evidence to support the current randomized trial funded by NINDS Health.” Results of that trial, which is comparing two doses of hydroxyurea — 20 mg/kg/day versus 10 mg/kg/day — for stroke prevention in 220 Nigerian children with SCA, are expected in 2021.

Funding for this study was provided by a National Institutes of Health R21 grant (1R21NS08063), Fogarty Center (R25 TW009337), Burroughs Wellcome Foundation, Phillips Family Donation, Aaron Ardoin Foundation for Sickle Cell Anemia, Vanderbilt endowed funds.

Najibah Aliyu Galadanci, MBBS, MPH, Bayero University/Aminu Kano Teaching Hospital, Kano, Nigeria, will present this study during an oral presentation on Saturday, December 3, 2016, at 12:15 p.m. PST Room 28ABCD of the San Diego Convention Center.

Webcast:

Eugenia Vicky Naa Kwarley Asare, et al.

1017 Prospective Implementation of Multi-Disciplinary Obstetric Team Decreases the Mortality Rate of Pregnant Women with Sickle Cell Disease in Ghana

Conclusions: In a low and middle income setting, a multidisciplinary team approach to care of pregnant women with SCD can dramatically decrease maternal mortality, as well as perinatal mortality. Further strategies must be employed to decrease the SCD related maternal mortality and perinatal mortality rates to levels expected in the non-SCD population and to implement multi-disciplinary SCD obstetric teams in other regions.

ASH Press Release: Implementing a multidisciplinary care team approach and establishing dedicated wards to care for pregnant women with sickle cell disease in Africa significantly reduces maternal and perinatal mortality after just 13 months, according to a study by researchers in Ghana.

“We saw a dramatic drop — close to a 90 percent reduction — in maternal deaths, which is really remarkable, especially in such a short period,” said lead author Eugenia Vicky Naa Kwarley Asare, MBChB, BSc, of the Ghana Institute of Clinical Genetics, Korle-Bu and the KorleBu Teaching Hospital in Accra, Ghana. “Sickle cell disease has acute and chronic complications, and to manage it well, especially in the context of pregnancy and childbirth, you need to have a number of specialists on board, including a hematologist.”

Dr. Asare says the obstetrics clinic at Korle-Bu Teaching Hospital sees approximately 250 pregnant women with SCD each year — up to 12 percent of whom die during pregnancy and after childbirth. In 2015, several efforts were put in place, including the assembly of a multidisciplinary care team with a dedicated hematologist to closely follow these women. Protocols were also put in place that included regular team meetings to discuss complex patients and to prevent and/or rapidly respond to any acute problems to help stem the tide of deaths. In this study, the researchers compared deaths and other outcomes before and after this intervention was put in place.

In the pre-intervention period (16 months), there were a total of 158 pregnancies in women with SCD

ranging from 18–43 years of age; 90 were included in the post-intervention period (13 months). Prior to the intervention, pregnant women with SCD received standard care, mostly by their obstetrician, and were admitted to multiple wards throughout the hospital. By contrast, women who received integrated care were evaluated by a multidisciplinary team including obstetricians with expertise in high-risk pregnancy, hematologists, pulmonologists, anesthesiologists, and nurses at enrollment, during all outpatient visits, and as any acute issues arose. They were closely followed until six weeks postpartum. Simple practices were put in place to prevent and manage acute issues including acute chest syndrome, which is a leading cause of death in these pregnant women, and acute pain episodes. The team also began routinely monitoring blood-oxygen saturation levels and performing Doppler ultrasounds and other tests for the fetus. Inpatient care was centralized to two designated wards to facilitate coordinated, rapid activation of medical services.

Analyses showed an 89 percent drop in maternal deaths (9.5% vs. 1.1%) and a 62 percent reduction in perinatal mortality (60.8% vs 23% per 1,000 total births) after a multidisciplinary SCD-obstetric team was activated.

Because there was not the same level of coordinated care and tracking of women prior to the multidisciplinary care teams being put in place, some data were incomplete, limiting comparisons. Still, the researchers will expand their approach to decrease maternal and perinatal mortality in other hospitals in Accra, Ghana. The strategy of including a multidisciplinary team with standard protocols for the care of pregnant women with SCD could have widespread public health benefits for pregnant women with SCD across sub-Saharan Africa and perhaps even in the United States where such clinics are not the norm.

Funding for the study was provided partly by Intramural Funds (Office of Research and Innovation), University of Ghana; Vanderbilt University Medical Center Gift Funds; Doris Duke Charitable Foundation; Burroughs Wellcome Foundation; Phillips Family Donation; Aaron Ardoin Foundation for Sickle Cell Anemia; and endowed chair funds from Vanderbilt University School of Medicine.

Eugenia Vicky Naa Kwarley Asare, MBChB, BSc, Ghana Institute of Clinical Genetics and the Department of Hematology, Korle-Bu Teaching Hospital in Accra, Ghana, will present this study during an oral presentation on Monday, December 5 at 5:00 p.m. PST in Room 6DE of the San Diego Convention Center.

Webcast: