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POSTER ABSTRACTS

113.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: BASIC AND TRANSLATIONAL

Longitudinal Characterization of Hemodynamic Changes with Multimodal Optical Techniques in Patients with Sickle Cell Disease Treated with Mitapivat

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The physiological impacts of sickle cell disease (SCD) are widespread and severe if left untreated. Sickled RBCs initiate vaso-occlusion (VOC) and have altered biomechanical properties that negatively affect blood rheology and microvascular hemodynamics in patients with SCD. Therapeutics can target different mechanistic pathways including reduction of hemoglobin S (HbS) polymerization, oxidative stress, or inflammation. There is an unmet need for non-invasive, point-of-care technologies that characterize the microvascular hemodynamics in SCD which could potentially broaden understanding of the underlying pathophysiology and supplement a clinician's ability to monitor therapeutic changes. Current clinical approaches can be time- and resource- intensive which limit their accessibility. Near-infrared spectroscopy (NIRS) is a non-invasive, optical technique that quantifies microvascular hemodynamics including hemoglobin (Hb) concentration, tissue oxygen saturation (StO_2), and blood flow (Cerussi et al, 2005). We evaluate the sensitivity of NIRS technologies to hemodynamic changes in patients with SCD undergoing treatment with mitapivat, an investigational oral allosteric activator of pyruvate kinase (PK), and compare the optical changes to changes in standard hematology markers with regard to the initial response and consistency of the response over time.

Fifteen patientswith HbSSwere enrolled in a study (ClinicalTrials.gov, NCT04610866) evaluating the long-term safety and tolerability of mitapivat in patients with SCD. We performed an optical hemodynamic assessment for each patient for a total of eight study visits over the span of a year including at baseline prior to drug initiation. NIRS probes were affixed to the forearm and forehead to collect hemodynamic information characteristic of brain and skeletal muscle while performing a brachial cuff occlusion challenge. We quantified concentration of oxy- and deoxy- Hb as well as StO_2 during the resting baseline prior to the occlusion. Additionally, we analyzed the post-occlusion reactive hyperemic response to assess vascular reactivity. Analysis was focused on quantifying the degree of change due to mitapivat treatment as well as the consistency of the response over the course of a year. Optical metrics were first compared against changes in Hb (Quang et, 2022) and then evaluated for consistency throughout the rest of the study period.

Nine out of 15 patients were assessed as baseline NIRS data were not available for six patients.We calculated optical hemodynamic metrics for all 72 measurement visits; two visits were excluded due to poor NIRS data quality. Figure 1A shows a typical measurement setup with NIRS probes acquiring simultaneous measurements from the forehead and forearm. Figure 1B compares the mean Hb level, mean forehead StO_2, and mean forearm StO_2 across the first year of treatment. Over the first six months, we observed an increase in forehead StO_2 from 56% to 60% and forearm StO_2 from 59% to 63%; blood Hb levels exhibited a similar increase going from 8.5 g/dL to 9.8 g/dL; this increase was sustained over the second six months for all three parameters. Average forehead StO_2 remained +3.6% above baseline while forearm StO_2 remained +1.7% above baseline at the end of a year.

NIRS can non-invasively provide objective measures of tissue composition, metabolism and vascular reactivity and can be performed in a simple manner with a series of simple perturbations.In this limited dataset, we have demonstrated that NIRS appears to reflect changes in Hb related to mitapivat both in response to an acute change and over an extended period.

Furthermore, we observed that on average, the NIRS responses were consistently elevated throughout the course of the year, mirroring what was observed in the blood Hb levels. Hemodynamic changes appear to be more easily observed in the brain rather than the skeletal muscle. Our data suggest that NIRS could be an adjunct for non-invasive hemodynamic monitoring in patients with SCD undergoing treatment.

Disclosures Xu: *Agios Pharmaceuticals, Inc.:* Other: US national principal investigator for the Phase 1 clinical trial pf AG-946 in patients with sickle cell disease.; *GlaxoSmithKline:* Membership on an entity's Board of Directors or advisory committees, Research Funding.

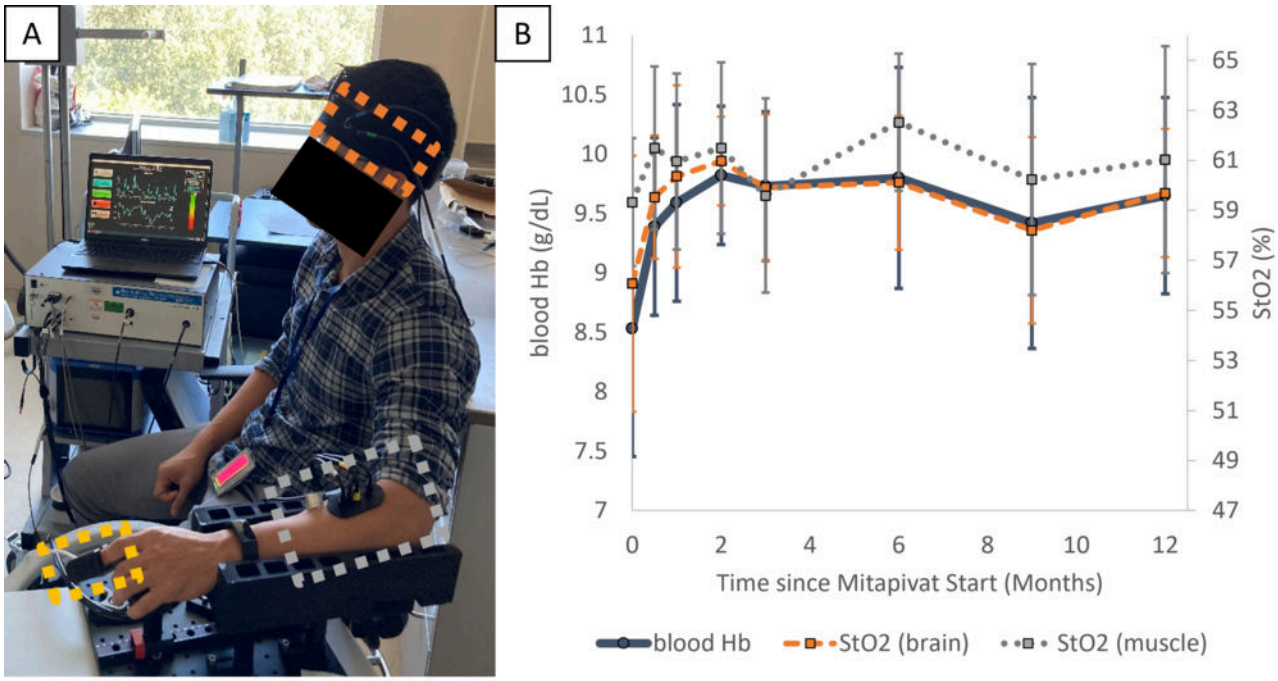

Figure 1: A) Photograph of healthy volunteer with NIRS probes affixed to the forehead (orange), forearm (gray), and fingertip (yellow) during a brachial cuff occlusion and B) hemodynamic data acquired from the forehead (orange) and forearm (gray) compared to blood Hb (blue)

Figure 1

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