INTRODUCTION

- Sickle cell disease (SCD) is characterized by vaso-occlusive pain episodes (VOEs).
- VOEs are subjective, thus difficult to use as a primary clinical endpoint in SCD.
- P-selectin supports pathological adhesive interactions critical mechanism in VOEs.1
- Inhibition of P-selectin in sickle mice lowered leukocyte-endothelial interaction and reversed acute vascular occlusion.2
- Transgenic sickle mice deficient in either P-selectin developed fewer vascular occlusions.3
- Citrazinium, an anti-P-selectin monoclonal antibody, reduced the annual rate of vaso-occlusive crises prospectively in a recent Phase 2 clinical trial.4
- Rovipasen, a pan-selectin inhibitor, decreased the length of active sickle crises.5
- A standardized P-selectin adhesion assay may be a useful prognostic biomarker for VOEs in SCD.

STUDY OBJECTIVES

- Determine the baseline variability whole blood (WB) and isolated white blood cell (WBC) P-selectin adhesion indices in individuals with SCD over time (6-months).
- Establish the relationship of whole blood (WB) and isolated white blood cell (WBC) P-selectin adhesion indices with self-reported baselines and VOEs in individuals with SCD.

METHODS

- 6-month observational cohort study in 35 SCD subjects (Fig. 1)
- Clinical baseline or VOE was determined using an electronic patient-reported (ePRO) tool.7
- In-home baseline blood samples were collected by a mobile phlebotomist every 3 weeks
- VOE sample were collected within 24 and 48 hours of self-report VOE (home, ED, or hospital), followed by another collection 2 days after VOE resolution, and baseline blood draw was resumed 2 weeks afterwards.
- Hematologic lab tests were conducted for all blood samples (Table 1).
- A standardized microfluidic flow-based P-selectin adhesion assay was performed on all blood samples at physiological flow conditions (1 dyn/cm², 1.67 Hz pulsatile flow, 37°C).
- Adhesion index was defined as the number of cells adhering within a fixed viewing area (cells/mm²).
- Linear regression and mixed model were used for statistical analysis by R software. p ≤ 0.05 was deemed statistically significant.

RESULTS

Figure 1. Schematic of study design.

Figure 2A. No significant difference between WB P-selectin adhesion index at baseline (n = 32, mean = 44 cells/mm²) vs. VOE (n = 5, mean = 46 cells/mm²) were observed based on mixed model analysis.

Figure 2B. WB P-selectin adhesion indices were significantly different at baseline (n = 32, mean = 163 cells/mm²) vs. VOE (n = 33, mean = 206 cells/mm²) based on mixed model analysis.

Table 1. Summary of significant correlations between adhesion indices and hematologic parameters

- The present P-selectin adhesion assay identifies the unique adhesive phenotype of individuals with SCD.
- WBC-adhesion indices on P-selectin were significantly higher during ePRO-validated VOES compared to pre-validated baseline conditions.
- Individuals with higher adhesion indices on P-selectin were more likely to have a VOE event sooner compared to individuals with lower P-selectin indices.
- Adhesion indices of WB and WBCs on P-selectin may be useful prognostic biomarkers for the likelihood and frequency of impending VOEs in individuals with SCD.
- The small number of subjects makes sub-group analyses challenging. These observations should be validated in a larger multi-center trial. Also, the annualized VOE rate was mathematically derived rather than through patient observation. Patients should be followed for >12 month in future study.
- Future Directions: We are developing predictive model for impending VOEs incorporating the P-selectin adhesion index. These models are underway to determine the relationship of adhesion indices to the clinical response to SCD-modifying therapy. It is plausible that clinical adhesion indices may prove to be surrogate endpoints for VOEs and other primary clinical endpoints in SCD.

CONCLUSIONS

References

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