Pan-selectin Antagonist GMI-1070 affects Biomarkers of Adhesion, Activation and the Coagulation Cascade in Sickle Cell Adults at Steady State

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Introduction: Engagement of selectins by their ligands leads to cellular activation and adhesion and plays a role in thrombus formation. In sickle cell disease (SCD), the selectins underlie vaso-occlusion, which results in vaso-occlusive crisis (VOC). In SCD patients high levels of soluble E-selectin (sEsel) are associated with increased mortality (Kato, BJH 2005). In addition, SCD patients exhibit chronic activation of the coagulation cascade and of leukocytes. Previously, we showed in animal models of SCD VOC that pan-selectin antagonist GMI-1070 reduced arrested RBC/WBC aggregates, and improved blood flow and survival. In a Phase 1 study of SCD adults at steady state (not in VOC), GMI-1070 inhibited neutrophil activation and platelet/neutrophil aggregate formation and increased circulating neutrophils. Herein we report on the effect of GMI-1070 on biomarkers of monocyte, endothelial cell, and coagulation cascade activation; and on the effect of hydroxycarbamide (hydroxyurea or HU) on these biomarkers for patients on this trial.

Methods: SCD adults at steady state (n=15) received an IV loading dose of GMI-1070 (20 mg/kg) and a second dose ten hours later (10 mg/kg). Safety and PK were reported elsewhere. HU use was noted. Biomarker blood samples were drawn prior to treatment, and at 4, 8, 24 and 48 hrs after the loading dose. Analytes measured included: soluble adhesion molecules sEsel, soluble P-selectin (sPsel) and intracellular adhesion molecule-1 (ICAM-1) by multiplex ELISA; tissue factor and thrombin-antithrombin complexes (TF and TAT) by ELISA; and, surface expression of monocyte β2 integrins MAC-1 & LFA-1; and platelet-monocyte aggregates (PMA) by flow cytometry. Expression levels were compared against pre-treatment, and stratified by HU use. Data are reported for 11 subjects (biomarkers) and 15 subjects (neutrophils).

Results: Soluble adhesion markers were reduced after 8 hrs (sEsel p=0.004; sPsel p=0.028; ICAM-1 p=0.004). Tissue factor (TF) was reduced at 4 (p=0.009) and 8 hrs (p=0.05). Thrombin-antithrombin complex (TAT) levels were reduced at all time points (p=0.002 at 4hr, 8hr, 24hr, 48hr). The percentage of PMA was reduced at 8 hrs (p=0.033). The expression of MAC-1 and LFA-1 was reduced at all time points (MAC-1, p<0.008 at 4hr, 8hr, 24hr, 48hr; LFA-1, p<0.008 at 4hr, 8hr, 48hr). When HU use was considered (HU–No; HU–Yes), the levels of sEsel, sPsel, ICAM-1, TF, TAT, MAC-1, and neutrophil counts were higher and more variable at baseline in the HU-No group, significantly so for ICAM-1 (p=0.048) and MAC-1 (p=0.001). After GMI-1070, significant reduction from baseline was seen in both groups: in the HU-No group for ICAM-1, TF, PMA, LFA-1, and in the HU-Yes group for sEsel, MAC-1, TF, TAT. Neutrophil counts increased at 24 hours in the HU-No group (p=0.001).

Conclusion: In this small sample of adults with SCD at steady state, selectin inhibition by treatment with GMI-1070 results in reduction in soluble adhesion markers, leukocyte activation, PMA, and markers of coagulation activation. This suggests that selectin inhibition affects downstream processes in vivo, continuing after clearance of >97% of the drug. This may represent interference in the processes that lead to VOC in SCD. A phase 2 study is underway to further explore the effect of this experimental drug on these markers and in the treatment of VOC.

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