3273 Pan-Selectin Antagonist, GMI-1070 Decreases Venous Thrombosis in a Mouse Model

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Daniel Durant Myers Jr., DVM, MPH[1*], Peter K. Henke, MD[1*], Jose A. Diaz, MD[2*], Shirley K. Wrobleski, BS[3*], Angela E. Hawley, MS[1*], Dallas Slack, BS[3*], Thomas W. Wakefield, MD[4*], John T. Patton, PhD[5*] and John L. Magnani[5]

[1]Surgery, University of Michigan, Ann Arbor, MI
[2]Surgery - Vascular Surgery, University of Michigan, Ann Arbor, MI
[3]University of Michigan, Ann Arbor, MI
[4]Department of Surgery, University of Michigan, Ann Arbor, MI
[5]GlycoMimetics, Inc., Gaithersburg, MD

Introduction: E- and P-selectin have structural similarities and both facilitate white blood cell tethering on vascular endothelium. The beneficial effect of combined E- and P-selectin inhibition in decreasing venous thrombosis (VT) by gene deletion in a mouse model of VT has been demonstrated. GMI-1070 is a pan-selectin inhibitor designed to mimic the bioactive conformation of the sialyl-Le^x carbohydrate binding domain of E-selectin and the sulfate interactions of P- and L-selectins. GMI-1070 has primary activity against E-selectin, with second and tertiary activity against P- and L-selectin. It has passed Phase I clinical trials showing no serious adverse events, and has a serum half-life in humans of 7 to 8 hours. In this study, the effect of pan-selectin inhibition by GMI-1070 on reducing VT was evaluated.

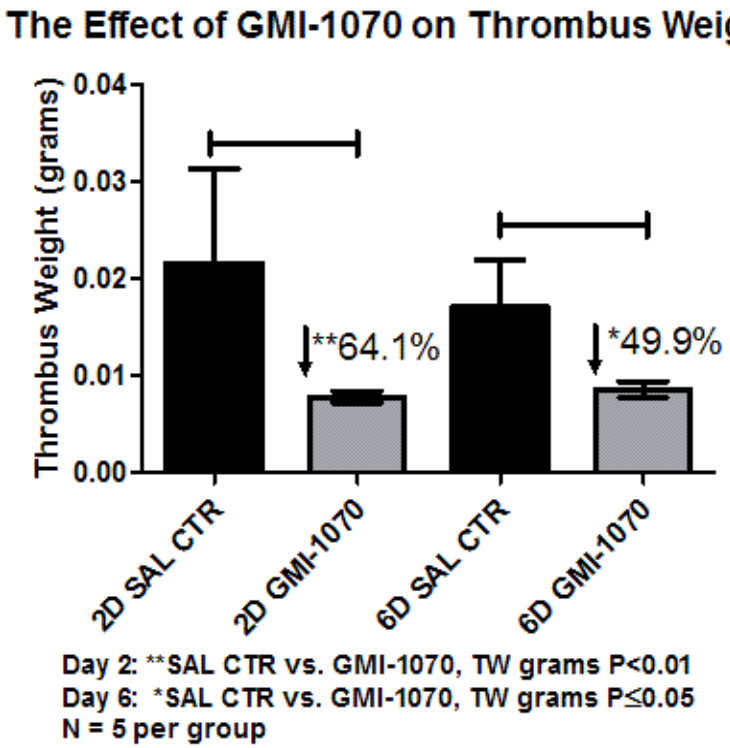
Methods: Male C57BL/6J mice (20-25grams) underwent our electrolytic IVC model (EIM) to produce a non-occlusive thrombosis via electrical free radical stimulation (250 μAmp) for 15 minutes. Experimental groups included the following: GMI-1070 delivered continuously by mini osmotic pump (300 mg/ml), and mice administered saline via the same protocol served as controls (SAL CTR). Continuous delivery of GMI-1070, or saline, began one day pre-thrombus induction. Mice were euthanized 2 and 6 days post-thrombosis for tissue harvest and blood collection for the following evaluations: thrombus weight (grams); plasma soluble E- and P-selectin (ng/mg total protein); vein wall E- and P-selectin protein by ELISA (pg/mg total protein); and vein wall inflammatory cell counts per high powered field.

Results: Continuous GMI-1070 administration significantly decreased venous thrombus weight (WT) two days post thrombosis (78±8 vs. 216±97 $x10^{-4}$ grams, $P<0.01$), and also significantly decreased TW six days post thrombosis versus saline controls (85±8 vs. 170±48 $x10^{-4}$grams, $P\leq0.05$) [Figure 1]. Circulating E-selectin protein was decreased significantly at both day 2 (21700±2014 vs. 56360±4284 pg/mg total protein, $P<0.01$), and day 6 (33070±3586 vs. 67310±2833 pg/mg total protein, $P<0.01$) post VT compared to respective saline controls. GMI-1070 significantly decreased vein wall E-selectin protein versus saline controls 6 days post

thrombosis (281±36 vs. 676±102 pg/mg total protein, P<0.02). No effect on vein wall P-selectin protein was noted. Vein wall inflammatory cell evaluation showed neutrophils peaking at day 2, then significantly decreasing by day 6 in these mice (23±5 vs. 7±1 Cells/5HPFs, P<0.01). Conversely, vein wall monocytes were found in significant numbers 6 days post thrombosis in mice receiving GMI-1070 versus saline controls (P<0.01). Both neutrophils and monocytes showed trends of increased vein wall extravasation versus saline groups.

Conclusions: GMI-1070 therapy significantly decreased venous thrombus formation. This pan-selectin inhibitor modulated circulating E- and P-selectin and vein wall E- selectin levels thus decreasing systemic and local inflammatory effects of both adhesion molecules. GMI-1070 therapy significantly increased vein wall monocytes and these mice had the greatest VT resolution. GMI-1070 has a high therapeutic potential for decreasing thrombosis and selectin related events.

Figure 1:



Disclosures: Patton: *GlycoMimetics, Inc.:* Employment, Equity Ownership. **Magnani:** *GlycoMimetics, Inc.:* Employment, Equity Ownership.