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E-Selectin Inhibition: A New Way to Treat Proximal Deep Venous Thrombosis

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Objective: There is a close inter-relationship between thrombosis and inflammation. In previous studies, we have shown the importance of P-selectin in thrombogenesis and thrombus resolution in many preclinical animal models. The role of E-selectin has been explored in rodent models and in a small pilot study of clinical calf vein deep venous thrombosis. The purpose of this study was to determine the role of E-selectin in thrombosis in a primate model of proximal iliac vein thrombosis, a model close to the human condition.

Methods: Iliac vein thrombosis was induced with a well-characterized primate model. Through a transplant incision, the hypogastric vein and iliac vein branches were ligated. Thrombus was induced by balloon occlusion of the proximal and distal iliac vein for 6 hours. The balloons were then deflated, and the primates recovered. Starting on postocclusion day 2, animals were treated with the E-selectin inhibitor GMI-1271, 25 mg/kg subcutaneously once daily (n = 4). Nontreated control (CTR) animals received no treatment (n = 5). All animals were evaluated by magnetic resonance venography (MRV), hematology (complete blood count), coagulation tests (bleeding time, partial thromboplastin time, activated partial thromboplastin time, fibrinogen, and thromboelastography) at baseline, day 2, day 7, day14, and day 21 with euthanasia. In addition, platelet function and CD44 expression on leukocytes were determined.

Results: E-selectin inhibition by GMI-1271 significantly increased vein recanalization by MRV vs CTR animals on day 14 ($P < .05$) and day 21 ($P < .0001$; Fig, *A*). GMI-1271 significantly decreased vein wall inflammation by MRV with gadolinium vein wall enhancement vs CTR also on day 14 ($P < .0001$) and day 21 ($P < .0001$; Fig, *B*). The thromboelastographic measure of clot strength showed significant decreases in animals treated with GMI-1271 vs CTRs at day 2 ($P < .05$) and day 7 ($P < .05$). Importantly, no significant differences in hematology or coagulation test results were noted between all groups, suggesting that E-selectin inhibition carries no bleeding potential. GMI-1271 did not affect platelet function or aggregation or CD44 expression on leukocytes. In addition, no episodes of bleeding were noted in either group.

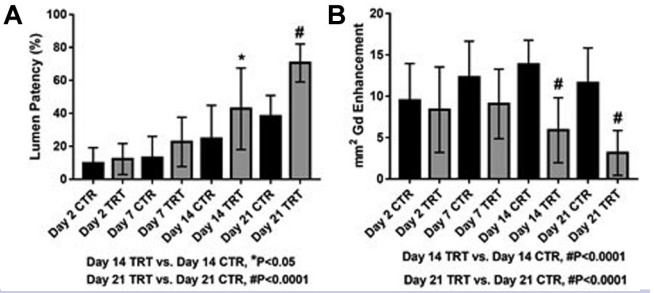

Fig. A, Percentage of vein recanalization. **B,** Vein wall inflammation. *CTR,* control; *TRT,* treated.

Conclusions: The study suggests that E-selectin modulates venous thrombus progression and that its inhibition will increase thrombus recanalization and decrease vein wall inflammation, without affecting coagulation. The use of an E-selectin inhibitor such as GMI-1271 could potentially change how we treat deep venous thrombosis.

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Association of Inflammatory and Hemostatic Biomarkers with Inflammasomes in Septic Patients at Risk for Development of Coagulopathy

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Objective: Sepsis is a catastrophic complication of infection that results in systemic inflammatory responses. Inflammasomes initiate the inflammatory cascade that results in the activation of caspase 1, leading to the upregulation of inflammatory cytokines such as interleukins B and 18. The NRLP-3 inflammasome contributes to the innate immune response identification of pattern recognition receptors on pathogens including bacteria and viruses. Whereas the role of inflammasome in the inflammatory response is known, it is not clear how inflammasome contributes to the hemostatic dysregulation observed in sepsis-associated coagulopathy. The purpose of this study was to quantitate inflammasome levels in defined sepsis-associated patients and to determine its potential relevance to various biomarkers of hemostatic dysregulation.

Methods: Plasma samples from 52 adults with sepsis and suspected coagulopathy were analyzed. Samples were collected from intensive care unit patients on day 0, under an Institution Review Board-approved protocol. Samples were stored at −80°C before analysis. Platelet count was determined as part of standard clinical practice. Healthy control samples were purchased from George King Bio-Medical (Overland, Kan). Prothrombin time and international normalized ratio were measured using recombiplastin reagent. Fibrinogen was measured using a clot-based method on ACL ELITE (Instrumentation Laboratory, Bedford, Mass) coagulation analyzer. Cortisol, D-dimer, plasminogen activator inhibitor 1 (PAI-1), NLRP-3 inflammasomes, microparticle-associated tissue factor, fibronectin, and CD40L were measured using commercially available enzyme-linked immunosorbent assays.

Results: In comparing patients with sepsis and suspected disseminated intravascular coagulation (DIC) with the normal plasma samples, there was a significant elevation in NLRP-3 inflammasome levels in the sepsis cohort ($P < .0001$). The Fig shows that the NLRP-3 inflammasome concentration in the sepsis cohort did not correlate with other biomarkers. An elevated level of NLRP-3 inflammasomes was significantly

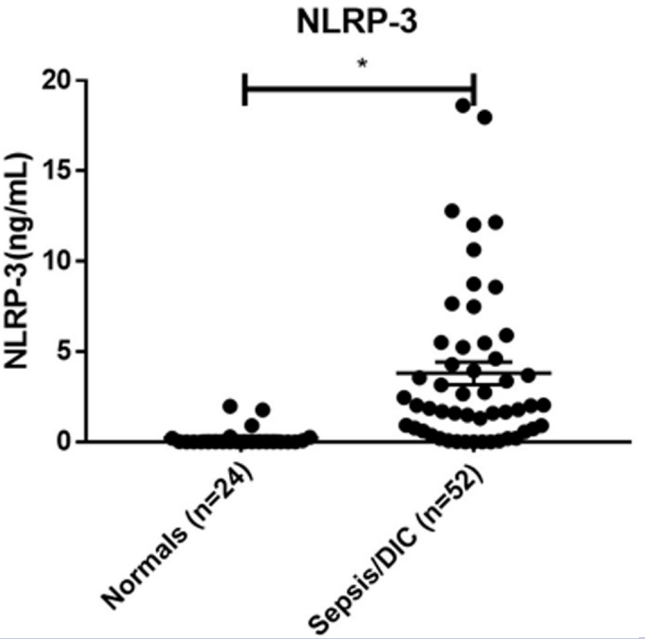

Fig. NLRP-3 inflammasomes in patients with sepsis and suspected disseminated intravascular coagulation (*DIC*) on day 0 (N = 52) compared with normal healthy controls (N = 24).