Anti-Selectin Therapy for Treatment of DVT: First Clinical Treatment

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Acknowledgements
This work has been supported by the contract HHSN268201400012C, part of the NHLBI Vascular Interventions/Innovations and Therapeutics (VITA) Program. The study drug, GMI-1271, was provided by GlycoMimetics, Inc.

No Disclosures

Endotoxin induced tissue factor (TF) mediated coagulation is enhanced in humans carrying the S128R E-selectin allele. (Jilma B et al, Blood 105:2380-2383, 2005)

Patients homozygous for the S128R E-selectin allele have an increased risk for VTE recurrence, highlighting the importance of E-selectin in venous thrombosis. (Jilma B et al, Arch Intern Med 166:1645-1649, 2006)

GMI-1271 Background

E-selectin antagonist, GMI-1271

Preclinical safety studies and a limited Phase 1 study in healthy volunteers had been completed prior to the start of the VITA study.

Presently, the compound is being evaluated for use in blood cancers (primarily AML) and other cancers that associated with elevated risk of metastasis.

E-Selectin Inhibitor (GMI-1271) small molecule antagonist
Aim 1 Trial Schematic (SAD phase)

GMI-1271 2-40 mg/kg IV over 20 min on Day 1
or
Lovonox 1mg/kg SQ x1 dose on Day 1
or
Saline 20mL IV over 20 min on Day 1

Follow up on Days 2, 3, 8 and 14

GMI-1271: n = 16
Lovonox: n = 4
Placebo: n = 4

Aim 2 Trial Schematic (MAD phase)

GMI-1271 10 or 20 mg/kg IV over 20 min every 24 hours on days 1-5
or
Lovonox 1mg/kg/d SQ every 24 hours on days 1-5

Follow up on days 8 and 19

Aim 3: Patient Selection

Inclusion Criteria
• Acute isolated calf vein DVT in the tibial, peroneal, gastrocnemial, soleal, and/or gastrocnemius veins
• Consent and intent to treat within 78 hours of confirmation of acute distal calf vein DVT by lower extremity duplex ultrasound and prior to anticoagulation.
• Age 18-75
• Male or Female
• Life expectancy >6 months
• Willing and able to participate in all required evaluations and procedures in this study protocol

Rationale for Studying Calf Vein DVT

60-70% of DVT are distal
• Complications include: proximal extension, VTE recurrence, PE, PTS
• Proximal extension subjects the patient to known risks of proximal VTE; rates range from 0-23% without AC and 0-44% on AC
• Clinical equipoise exists, with controversy regarding the need for anticoagulation
• Very heterogeneous studies and populations; CACTUS trial (results presented 6/15, Righini M et al, Lancet Hematology 3:e556-e562, 2016) did not suggest any advantage to upfront anticoagulation in 252 patients, with more bleeding.
Aim 3 Trial Schematic

GMI-1271 20 mg/kg/day IV over 20 min on Treatment days 1-5
Lovenox 1.5 mg/kg/day SQ every 24 hours on Treatment days 1-5
Repeat Doppler LE day 8 and 19 Follow up on Days 8 and 19

Summary (Aim 1 and 2)
• No Serious AEs Reported
• Enoxaparin increased R and K time and decreased Angle compared to GMI-1271; suggesting increased bleeding risk with enoxaparin
• sEsel trends lower in GMI-1271 treated subjects as expected for on-target effects
• Lower leukocyte and platelet activation in GMI-1271 treated volunteers compared with Enoxaparin (evidenced by MPO and MAC-1 measurements)

Patient 2
• 55M who experienced pain in posterior calf after extensive traveling and driving. Presented to his FP on with elevated D-dimer, calf swelling and tenderness.
• LE duplex: LLE: totally occluding one of paired posterior tibial veins (with the second PT vein patent).
• Consented to protocol, and meet eligibility criteria
• Randomized to GMI-1271
• No AE or safety concerns with treatment
Conclusions

VTE is a very common problem (3rd most common cardiovascular disease behind MI and Stroke) and most common cause of in-hospital death.

Current drugs all carry significant bleeding complications and do not prevent PTS.

Targeting E-selectin is a new strategy to treat VTE, significantly lower bleeding, and decrease vein wall fibrosis.

Thank You