TRANSLATIONAL SCIENCES

Factor XI Inhibition for the Prevention of Catheter-Associated Thrombosis in Patients With Cancer Undergoing Central Line Placement: A Phase 2 Clinical Trial

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Background (I)

- Despite the ubiquitous utilization of central venous catheters in clinical practice, their use commonly provokes catheter-associated thrombosis (CAT).
- Asymptomatic CATs occur in up to 66% of screened individuals who receive a central line, and rates of symptomatic catheter thrombosis range from 5% to 41% in patients with cancer.
- It has been suggested that activation of the contact activation pathway of coagulation plays an integral role in the development of CAT.
- As such, targeting this particular aspect of the coagulation cascade may be useful for managing thrombosis without an increased bleeding risk.

Background (II)

- Gruticibart is a recombinant humanized monoclonal antibody targeting the apple 2 domain of FXI.
- It only prevents FXIIa mediated contact activation of FXI, while allowing FXI to be activated through alternative pathways (eg, autoactivation).
- In prior studies, this antibody has been shown to be safe and well tolerated with no reported serious drug related adverse events or clinically relevant drug-related bleeding.

AIM of the study

- To evaluate the safety and efficacy of the anti-FXI inhibitor gruticibart in patients with cancer receiving central line placement.

Methods (I)

- Ambulatory cancer patients undergoing central line placement were enrolled.
- Patients were excluded if they had acute leukemia, glomerular filtration rate of <60 mL/min per 1.73 m2 of body surface area, hepatic dysfunction (liver function tests >2× the upper limit of normal or Child-Pugh class B or C), coagulopathy (international normalized ratio >1.5 or prolonged activated partial thromboplastin time [aPTT]), history of intracranial hemorrhage, history of primary brain tumor or known metastases, or a known bleeding diathesis.
- Patients received a single dose of gruticibart (2 mg/kg) administered through the venous catheter within 24 hours of placement.
- A parallel, noninterventional study was used as a comparator.

Methods (II)

- In total, 22 patients were enrolled: 11 patients in the FXI inhibitor intervention trial and 11 patients in the noninterventional trial.
- At 14±7 days a compression ultrasound was performed in all patients.
- Blood samples were collected before central line placement (visit 1) and at the time of surveillance ultrasound at 14±7 days (visit 2) following central line placement.
- Patients were monitored for 30 days following enrollments to evaluate for adverse events.

Results (I)

- Patients in the interventional study had a mean age of 56 years. The most common malignancy was pancreatic cancer (36%), followed by colorectal cancer (27%) and lymphoma (18%). At the time of enrollment, 27% of patients had stage IV cancer.

- In the comparison control study, patients had a mean age of 64 years. The most common malignancy was lymphoma (36%), followed by colorectal cancer (27%) and head and neck cancer (27%). At the time of study enrollment, 54% of patients had stage IV cancer.

Results (II)

- In the interventional study, the mean aPTT was significantly prolonged following treatment with the anti-FXI, gruticibart while in the control study, there was no change in aPTT between visits.
- No difference in platelet activation following administration of gruticibart was observed.
- During the study period, a nonocclusive CAT was detected at the time of ultrasound in 1 patient (12.5%) in the intervention study and in 4 patients (40.0%) in the control study. No symptomatic CATs occurred in either study during the study period.

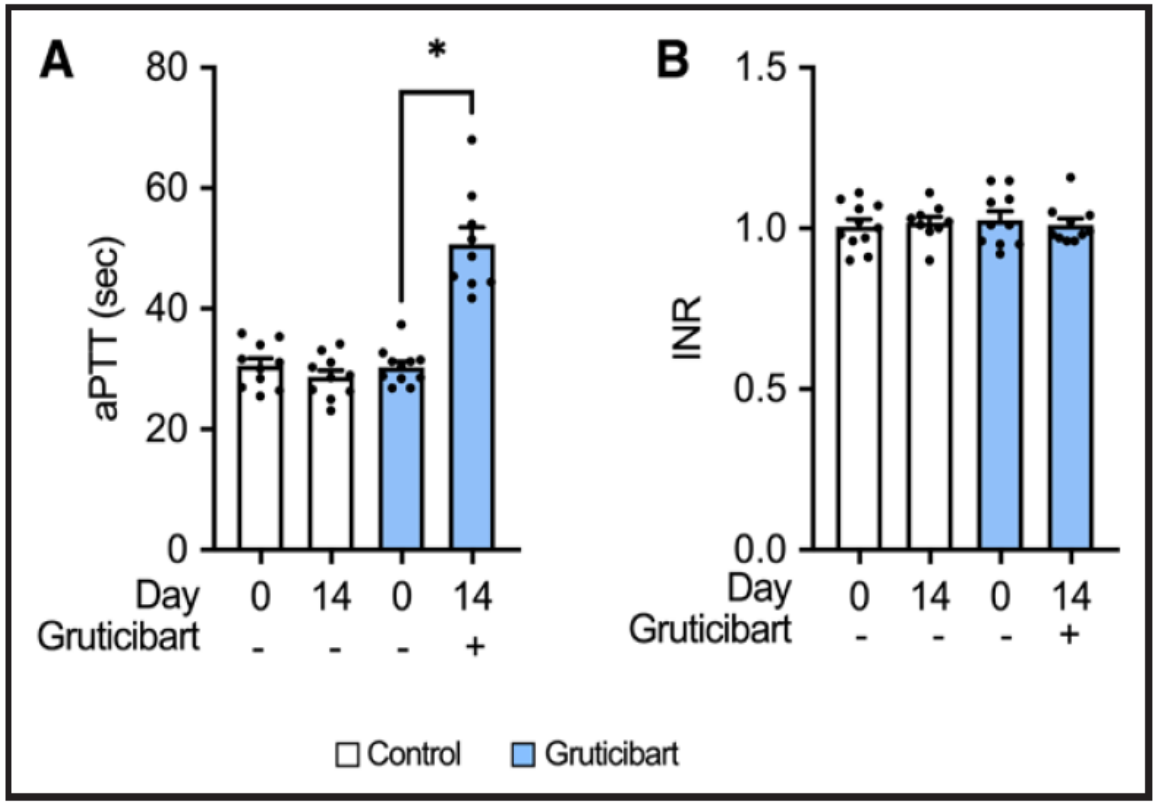

Figure 2. Effect of the anti-FXI (factor XI) antibody, gruticibart, on the coagulation profile following central line catheter placement.

Activated partial thromboplastin time (aPTT; **A**) and international normalized ratio (INR; **B**). White bars denote control study, and blue bars represent intervention study. Baseline (day 0) is compared with 2 weeks after administration of gruticibart (day 14) using paired *t* tests. *$P<0.05$ ($P=0.0004$ [**A**], $P=0.60$ [**B**]).

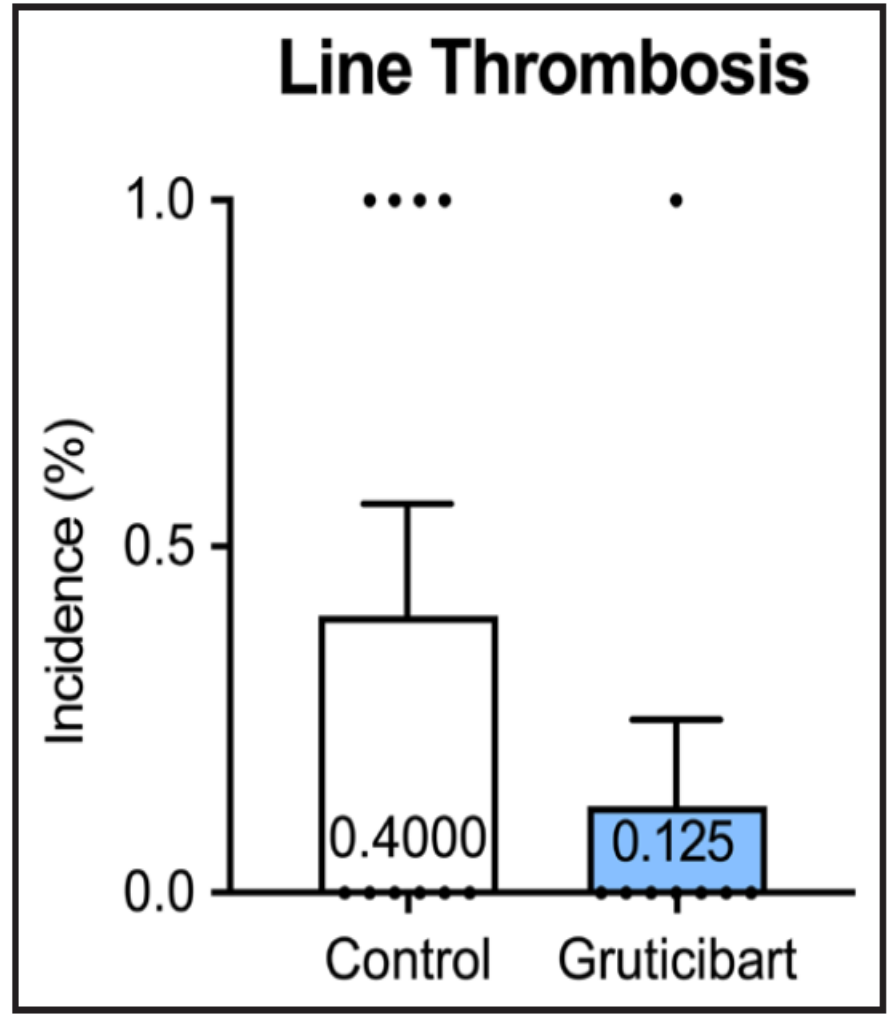

Figure 3. Effect of the anti-FXI (factor XI) antibody, gruticibart, on the incidence of asymptomatic, nonocclusive mural thrombosis at the time of the surveillance ultrasound (day 14) in intervention and control studies.

Data are presented as mean±SEM.

Results (III)

- Gruticibart was well tolerated and without infusion reactions, drug-related adverse events, or clinically relevant bleeding.
- T(thrombin)-AT (antithrombin) and activated FXI–AT complexes increased following central line placement in the control study, which was not demonstrated in the intervention study.
- CRP (C-reactive protein) did not significantly increase on day 14 in those who received gruticibart, but it did significantly increase in the noninterventional study.

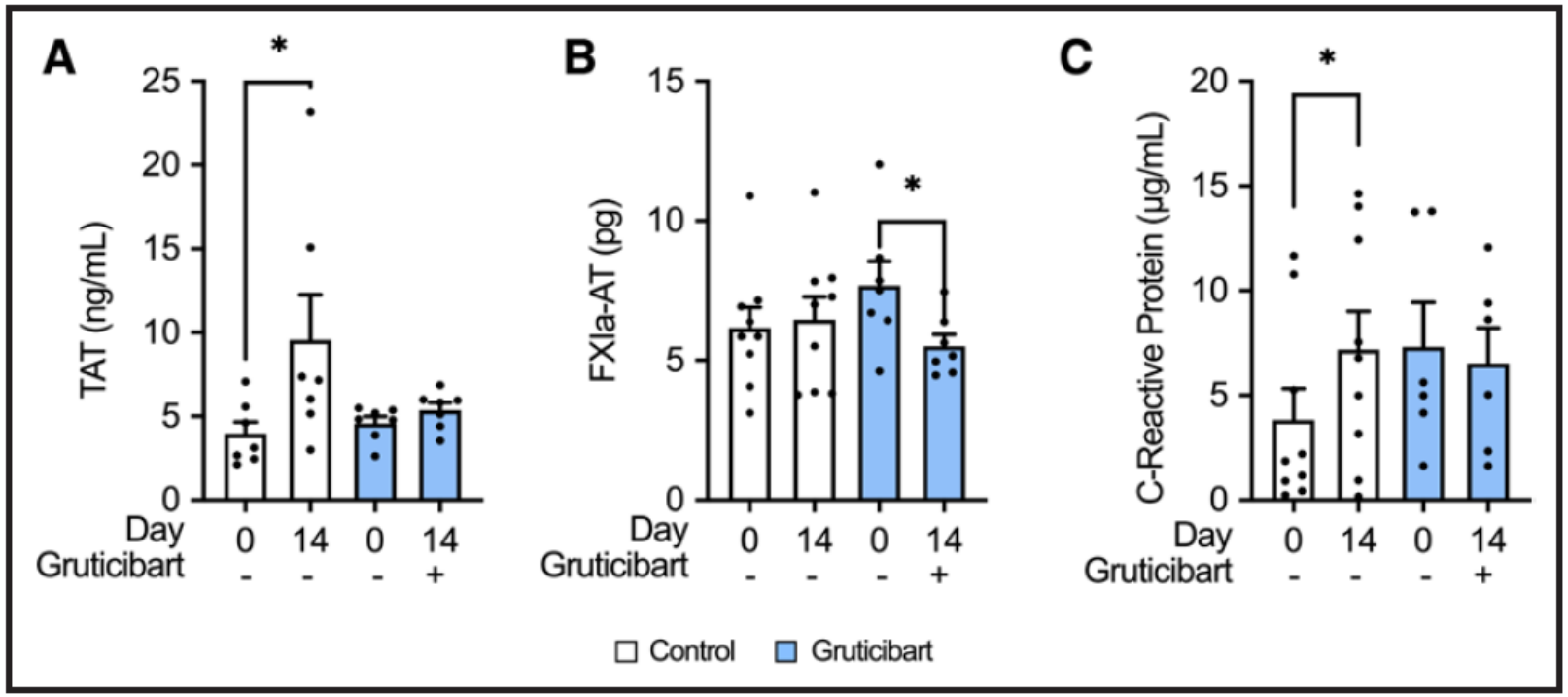

Figure 4. Effect of the anti-FX (factor XI) antibody, gruticibart, on markers of activation of coagulation and systemic inflammation..

Effect of the anti-FXI (factor XI) antibody, gruticibart, on thrombin-antithrombin (TAT) complexes (**A**), activated FXI (FXIa)–AT (antithrombin) complexes (**B**), and a marker of systemic thromboembolism, CRP (C-reactive protein; **C**), in patients with a central line. Data are presented as mean±SEM. White bars denote control group, whereas blue bars represent the intervention group. Baseline (day 0) is compared with 2 weeks after administration of gruticibart (day 14) using paired *t* tests except for comparisons between day 0 and day 14 for the intervention group on **C** via the Wilcoxon signed-rank test. *$P<0.05$ ($P=0.0335$ [**A**], $P=0.0458$ [**B**], $P=0.0195$ [**C**]).

Conclusions

- This study suggest that pharmacological agents that prevent FXIIa mediated contact activation of FXI, such as gruticibart, can be safely administered in patients with cancer and may reduce the incidence of catheter thrombus associated with central line placement.
- The trial determined that 2 mg/kg of gruticibart was well tolerated, without specific drug-related adverse events in the medically complex population of patients with cancer receiving chemotherapy.
- Interestingly, gruticibart also appeared to mitigate the generation of TAT complexes and increases in CRP after central line placement.
- The extent to which FXIIa-mediated activation of FXI may contribute to systemic cancer-associated thrombosis and the impact that sequential gruticibart administration may have on the longitudinal rates of deep vein thrombosis and pulmonary embolism in patients with cancer remains a critical, unanswered question.