Turning Up to Eleven: Factor XI Inhibitors as Novel Agents to Maximize Safety and Maintain Efficacy in Thromboembolic Disease

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Abstract: Within the past decade nonvitamin K oral anticoagulants have emerged as the standard of care for the prevention and treatment of thromboembolic disorders, however safety of anticoagulants remain a concern for many patients and providers. There exists new interest in factor XI inhibition as novel therapeutic target based on observations of lower thrombotic rates and without significant bleed risk in individuals with inherited factor XI deficiency. Several classes of factor XI inhibitors including antisense oligonucleotides, monoclonal antibodies, and small molecule inhibitors have undergone preclinical studies and clinical trials in humans. Both osocimab and IONIS-FXI have been evaluated in patients undergoing orthopedic surgery and demonstrated superiority to enoxaparin without increasing major bleeding. Future studies with both these agents are ongoing, as well as the continued development of other inhibitors of factor XI. Early data regarding factor XI inhibition is encouraging as a potent anticoagulant and may offer a safer alternative compared to therapeutic currently available in contemporary practice for thromboembolic disease. (Curr Probl Cardiol 2021;46:100696.)

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Introduction

The role of anticoagulant-based prevention of thromboembolic events with vitamin K antagonists and parenteral agents including unfractionated heparin, low-molecular-weight heparin, and fondaparinux is well established.[1] The revolution over the past decade in clinical practice brought on the emergence of nonvitamin K oral anticoagulants (NOACs), specifically targeting either factor Xa or direct thrombin inhibition for a wide array of indications including treatment of venous thromboembolism (VTE), stroke prevention in atrial fibrillation, and VTE prevention following orthopedic surgery. Major guidelines now recommend these agents in preference to warfarin, as they provide similar efficacy and provide a significant safety benefit.[2-4] However, both factor Xa inhibitors and direct thrombin inhibitors are associated with risk of bleeding and often complicated by the lack of availability of a clear reversal agent. In randomized studies of patients with atrial fibrillation, factor Xa inhibition with either apixaban or rivaroxaban resulted in annual rates of major bleeds of 2.13% and 3.6%, respectively. While the overall number of major bleeds is lower compared to traditional vitamin K antagonist therapy, this still poses a safety concern.[5,6] Furthermore, approximately 28,000 deaths annually can be attributed to factor Xa-related major bleeds.[7] While NOACs clearly provide advantages in terms of less frequent monitoring, less injections, and less intracranial bleeding, significant risks to patients remain with the current anticoagulant treatment options.

Factor XI (FXI) has garnered attention as a potential drug target based on observations in patients with inherited FXI deficiency or as a biomarker in the general population. FXI plays a role in the clotting cascade by contributing to homeostasis activating FXI. In the instance that FXI is inhibited, it can lead to a disruption in the clotting cascade and prevent the formation of a thrombus. FXI deficiency, otherwise known as hemophilia C, is a congenital bleeding disorder that affects both men and women.[8] Contrary to hemophilia A (factor VIII) or B (factor IX), FXI deficiency is generally associated with less spontaneous bleeding; however, patients remain highly susceptible following serious trauma. In regards to thrombosis risk, FXI deficient patients may display inherent protection. In a cohort of 115 Ashkenazi Jews with FXI deficiency, ischemic stroke was significantly less frequent compared to the general Israeli population. However, in a prior study there was no difference found in the incidence of myocardial infarction.[9,10] FXI deficiency appears to also confer protection against deep vein thrombosis (DVT). In a cohort of 219

patients with FXI deficiency, no patients developed DVT, which was significantly lower than expected with population controls.[11]

At the other end of the spectrum, elevations in FXI may signify those at increased risk of thrombosis. In the Longitudinal Investigation of Thromboembolism Etiology, elevations of FXI in the top quintile were associated with a 2-fold increase in VTE.[12] This supported prior findings from the Leiden Thrombophilia Study, in which FXI levels in the top decile were also associated with greater than 2-fold increase.[13] A retrospective case-control study reported as high as a 5-fold risk in VTE and 4-fold increase in stroke or transient ischemic attack in patients with FXI levels above the 95th percentile.[14] The Atherosclerosis Risk in Communities study prospectively evaluated ischemic stroke and associated factor levels (Factor II, V, IX, X, XI, XII, plasminogen and 2-antiplasmin). Only elevated FXI levels were associated with increased stroke risk following multivariate analysis.[15] As suggested by data in FXI deficiency, the evidence supporting FXI's role as a biomarker in coronary thrombosis is less clear. In the Study of Myocardial Infarctions Leiden, elevated FXI in the top quintile was associated with a 1.8-fold increase in myocardial infarction; however this association was not evident in the Risk of Arterial Thrombosis In relation to Oral contraceptives study or the Second Northwick Park Heart Study.[16-18] Based on data in both FXI deficiency and abnormal elevations, the role of pharmacologic inhibition of factor FXI may be useful in the prevention of VTE and ischemic stroke.

Pharmacologic Agents and Animal Studies

Major therapeutic targets currently under investigation and development can largely be categorized as antisense oligonucleotides (ASO), monoclonal antibodies, and small molecules. IONIS-FXI (formerly ISIS 416858) is an ASO that targets FXI by binding FXI messenger RNA (mRNA) in the liver. IONIS-FXI bound to FXI mRNA results in mRNA degradation and prevents factor synthesis resulting in a reduction of FXI activity.[19] Preclinical studies with IONIS-FXI in mice and primate models demonstrated potent antithrombotic effects with $\geq$ 50% reduction of plasma FXI levels, without an increased risk of bleeding.[19-21]

Currently, the monoclonal antibodies, osocimab (BAY-1213790), xisomab 3G3 (AB023), and abelacimab (MAA868) have completed clinical trials, which will be discussed in further detail below.[22-24] Osocimab is a fully human monoclonal IgG1 antibody that inhibits FXIa through allosteric inhibition and thus prevents activation of factor IX.[25] In rabbit models, osocimab did not increase bleeding time or blood volume, yet was able to

inhibit thrombus formation.[26] Xisomab 3G3 is a humanized monoclonal antibody developed from a murine IgG2b monoclonal antibody (14E11) in which both inhibit FXI activation indirectly via FXII without altering the feedback activation of FXI via thrombin.[27,28] Mice pretreated with 14E11 prior to induction of acute ischemic stroke had smaller infarct size, increased reperfusion and improved neurological performance. Pretreatment had no effect on impaired hemostasis and did not reduce mortality.[29] Aximab (O1A6), a specific neutralizing monoclonal antibody to FXI, prevented graft occlusion without affecting bleeding times compared to aspirin in a baboon model.[30] Abelacimab is a fully human monoclonal antibody that binds with high affinity to both FXI and FXIa, and similar to the other aforementioned compounds above, displayed promising anticoagulant activity in mice and primate models without significant bleeding.[24] Additional data is available with several other monoclonal antibodies against FXI (αFXI-175, αFXI-203, C24, and DEF) which display similar in vitro and animal data as others in the class[31,32]

Several small molecules are currently in development and have yet to complete early clinical trials. Bristol-Myers Squibb has multiple compounds in their pipeline (BMS-262084, BMS-654457, BMS-724296, BMS-986177, and BMS-962212). BMS-262084 is a mechanism-based inhibitor that binds to the active site of human serine proteases with a high affinity for FXIa, which demonstrated a 38% reduction of thrombus weight following $FeCL_2$-induced venous thrombosis, without significant prolongation of bleeding times in a rabbit model.[33,34] However, due to the irreversible nature of inhibition with BMS-262084 and concern for reversal may be necessary in clinical practice, future development continued with reversible inhibitors such as, BMS-654457. BMS-654457 inhibited carotid artery thrombosis in the rabbit model with limited effects on bleeding time.[35] ONO Pharmaceuticals also has several small molecule FXI inhibitors that have underwent clinical investigation. ONO-7750512, ONO-5450598, and ONO-8610539 have demonstrated efficacy in rabbit and monkey thrombosis models without an increase in bleeding.[36-39] Both ONO-8610539 and argatroban improved neurological outcomes and infarct size in mice with induced MCA stroke, however only ONO-8610539 did not increase cerebral hemorrhage volume.[40] Other small molecules (BMS-962212, BMS-986177 and EP-7041) have progressed to first-in-human studies and will be discussed in the next section.

Early research continues with compounds of different drug classes including aptamers, allosteric inhibitors, natural inhibitors and even the potential for an FXI vaccine.[41] While many of these compounds have

early results in animal studies similar to the agents in the classes above, others have not yet progressed.

Clinical Trials of FXI Inhibition

Antisense Oligonucleotides

The first trial to evaluate FXI-ASO therapy with IONIS-FXI in healthy volunteers demonstrated significant reductions in FXI activity with both a single dose (50, 100, 200, or 300 mg) and multiple ascending doses over 6 weeks. IONIS-FXI significantly prolonged the activated partial thromboplastin time (aPTT), which correlated with reduced FXI activity and had an estimated half-life of approximately 20 days. No bleeding events were reported, however more subjects experienced mild injection-site reactions compared to placebo (33% vs. 10%).[42] With early data to suggest safety and tolerability, the FXI-ASO total knee arthroplasty study set out to evaluate the potential of FXI inhibition for thrombosis prevention after orthopedic surgery.[43] Patients aged 18 years or older undergoing primary unilateral total knee arthroplasty were included and randomized to 1 of 3 IONIS-FXI (FXI-ASO) dosing regimens (100, 200, or 300 mg) or enoxaparin 40 mg. Following initial enrollment, a protocol amendment halted use of the 100-mg dose to ensure adequate reduction in FXI levels both prior and following surgery. The dosing algorithm for IONIS-FXI began 5 weeks prior to surgery. The first dose was given subcutaneously (day 1) followed by doses on day 3, 5, 8, 15, 22, 29, and the final dose on the day of surgery (day 36), administered 6 hours postoperatively. Enoxaparin 40 mg was given subcutaneously at the discretion of the investigator either the evening before surgery or 6-8 hours postoperatively. The primary endpoint was evaluated 8-12 days postoperatively, for the composite of asymptomatic DVT, symptomatic VTE, fatal PE, or unexplained death in which PE could not be ruled out. The primary safety outcome was a composite of major bleeding or clinically relevant nonmajor bleeding. Major bleeding was defined as either fatal, occurring in a critical area or organ, overt bleeding requiring transfusion of 2 or more packed red blood cells or surgical site requiring re-intervention. Clinically relevant nonmajor bleeding was defined as overt bleeding not meeting the criteria for major but required medical evaluation, intervention or resulted in clinical consequences.

A total of 300 patients underwent randomization, however only 274 patients were included in the per-protocol analysis with objective

confirmation of a symptomatic event or asymptomatic event by venogram, and without significant protocol deviations. The primary outcome occurred in 30% of the enoxaparin group, 27% of the IONIS-FXI 200-mg group, and only 4% in the IONIS-FXI 300-mg group. Both IONIS-FXI doses demonstrated noninferiority and the 300-mg dose proved to be statistically significantly superior to enoxaparin in regards to the primary endpoint ($P < 0.001$). Symptomatic DVT occurred in 3 patients, 1 with enoxaparin and 2 in the IONIS-FXI 200-mg group. Overall, there were no pulmonary embolism or deaths in any treatment group. Major or clinically relevant nonmajor bleeding was similar among groups. The primary safety outcome occurred in 8% of patients in the enoxaparin group and 3% in each of the IONIS-FXI groups. Injection-site reactions were more common with IONIS-FXI, however these did not lead to study drug discontinuation.

FXI activity was measured to correlate with the primary outcome events with a cutoff of FXI activity $\leq$0.2 U/mL as laboratory evidence for antithrombotic effect. At the time of surgery FXI levels were 0.02 $\pm$ 0.01 U/mL in the IONIS-FXI 300 mg group, 0.38 $\pm$ 0.01 U/mL in the IONIS-FXI 200-mg group and 0.93 $\pm$ 0.02 in the enoxaparin group. These laboratory findings may likely explain the superiority finding with the 300-mg dose. In patients that received the 300-mg dose, 59.2% achieved the $\leq$0.2 U/mL threshold compared to 14.9% of patients who received the 200-mg dose. Overall, the reduction of VTE was driven by those who met the FXI activity reduction with IONIS-FXI compared to those who did not (4.8% vs 25.2%). This trend was also evident as an approximate 3-fold increase in the primary outcome when examining individual dosing regimens with both the 300 mg (2.4% vs 6.9%) and 200-mg dose (10.0% vs 29.8%).

A subsequent study of pharmacokinetics (PK) and pharmacodynamics (PD) for both single 300-mg dose and multi-dose 12-week regimens (200 or 300 mg) was performed in 49 patients with end stage renal disease on dialysis.[44] Over the course of 12-week treatment, PK data did not suggest accumulation with hemodialysis, with a drug half-life of approximately 2 weeks. Similar to prior studies, IONIS-FXI-LRx prolonged the aPTT in a dose-dependent manner, and reduced FXI activity. Dialysis circuit clotting events were significantly reduced in all 3 groups. With reported events in 20% of the 300-mg group, 40% in the 200-mg group and 62% of the placebo group, specifically in patients in whom achieved FXI activity <0.4 U/mL. Overall, there were no major or clinically relevant nonmajor bleeding events, however minor bleeds associated with arteriovenous fistula/graft sites were reported in the 300-mg dose cohort.

Monoclonal Antibodies

Based on success in animal studies, several monoclonal antibodies targeting FXI have progressed to human studies. Recently, MAA868 published first-in-human results in healthy volunteers.[24] This study was a randomized, single-center, single-ascending dose study to assess safety, tolerability and, PK/PD. Dosing cohorts were 5, 15, 50, 150, and 240 mg administered subcutaneously. Severely obese subjects (body mass index >35 kg/m^2) were only enrolled in the 240-mg dose cohort. FXI activity reduction $\geq 80\%$ and aPTT prolongation >2-fold were sustained for >4 weeks in the 150 mg (29 days) and 240-mg dose (57 days). Severe obesity slightly attenuated the duration of effect compared to healthy weight, however effect sustained >4 weeks also. Three serious adverse events occurred in 2 total patients, one of which resulted in death; however, it was determined that none of these were related to MAA868 treatment. MAA868 was well tolerated, in which no participants reported injection site reactions and the most common reported adverse effect was headache. Based on these positive results further clinical investigation is ongoing as potential once monthly subcutaneous anticoagulant in patients with atrial fibrillation (NCT04213807).[45]

Xisomab 3G3 has reported phase 1 clinical safety, tolerability, and PK/PD data in 21 healthy volunteers.[46] Single bolus IV doses of 0.1, 0.5, 2, and 5 mg/kg were administered based on randomized assignment. Xisomab 3G3 substantially prolonged the aPTT by roughly 2-fold for approximately 2 and 4 weeks in the higher dose cohorts (2 and 5 mg/kg, respectively). Neither bleeding time or prothrombin time were affected. Xisomab 3G3 was well tolerated with 44% of participants experiencing treatment-emergent adverse advents compared to 60% of participants with placebo.

The first to evaluate FXI inhibition with antibody therapy in healthy volunteers and in a targeted disease state was osocimab. In phase 1 study, 9 single IV doses were studied (0.015, 0.06, 0.15, 0.30, 0.60, 1.25, 2.50, 5.0, or 10.0 mg/kg) which demonstrated dose-dependent effects of the aPTT, clotting time, but not bleeding time. There were no reported bleeding events, hypersensitivity, and low potential for immunogenicity.[47] Further study with osocimab continued in the phase 2 FXIa Inhibition for the Prevention of Venous Thromboembolism in Patients Undergoing Total Knee Arthroplasty (FOXTROT) study.[48] Patients were included if they were 18 years or older and undergoing elective primary unilateral total knee arthroplasty. Patients were initially randomized in an open-label fashion to receive 1 of 4 osocimab doses (0.3, 0.6, 1.2, or 1.8 mg/kg) given

postoperatively on the day following surgery or to receive 1 of 2 comparators (enoxaparin 40 mg once daily or apixaban 2.5 mg twice daily). A subsequent second phase introduced preoperative dosing arms of 2 osocimab doses (0.3 or 1.8 mg/kg) administered the day prior to surgery for evaluation. The primary endpoint was evaluated 10-13 days postoperatively, for the composite of asymptomatic DVT, symptomatic DVT, fatal or nonfatal PE, or unexplained death in which PE could not be ruled out. The primary safety outcome was a composite of major bleeding or clinically relevant nonmajor bleeding evaluated at 10-13 days postoperatively.

A total of 813 patients underwent randomization, however only 600 patients were eligible for the per-protocol analysis with objective confirmation of a symptomatic event or asymptomatic event by venogram, and without significant protocol deviations. The primary outcome occurred in 26.3% of patient receiving enoxaparin and 14.5% receiving apixaban. Postoperative doses of osocimab 0.6, 1.2, and 1.8 mg/kg demonstrated noninferiority with primary outcome rates of 15.7%, 16.5%, and 17.9%, respectively. Both postoperative and preoperative administration of osocimab 0.3 mg/kg failed to meet the non-inferiority margin with event rates of 23.7% and 29.9% respectively. Preoperative osocimab dosing of 1.8 mg/kg was superior to enoxaparin (11.3% vs 26.3%; $P = 0.007$). Major or clinically relevant nonmajor bleeding was low for the osocimab regimens. The primary safety outcome occurred in 0% of patients in the 0.6 mg/kg group, 1% in the 1.2 mg/kg group, 2% in those receiving 0.3 mg/kg (postoperatively) and 3% in the 1.8 mg/kg group (postoperatively). Preoperative regimens were also similar with 1.9% of patients experiencing the composite bleeding outcome in the 0.3 mg/kg group and 4.7% in the 1.8 mg/kg group. All bleeds were related to surgical site and only one was classified as a major bleed, which occurred with the 1.8 mg/kg preoperative dosing regimen.

Small Molecule Active Site Inhibitors

To date, clinical evaluations of small molecule inhibitors in humans have been limited to healthy volunteers. EP-7041, a selective FXIa inhibitor, was evaluated in single ascending doses and with continuous infusion for safety, tolerability, and PK/PD in 60 adult participants.[49] Single doses ranged from 0.01 to 1.0 mg/kg and continuous infusions ranged from 0.01 to 0.6 mg/kg/h for a 5-day duration. EP-7041 exhibited rapid onset and offset as reflected by prolongation of the aPTT of 2.2-fold in the single 1.0 mg/kg and 1.7-fold in the 0.6 mg/kg/h continuous infusion arm. No serious adverse events or clinically significant bleeding occurred

in any dosing arm, although headaches (7%) and injection site reactions (23%) were common. With established safety and tolerability, EP-7041 is pursuing phase 2 studies in a cardiac surgery population.[50]

Phase 1 human studies with BMS-962212 examining PK/PD, tolerability, safety were also recently reported.[51] BMS-962212 was evaluated in 2 parts with 4 dosing panels per part, first as single IV infusion of 2 hours (1.5, 4, 10, and 25 mg/h) and second as a continuous infusion over 5 days (1, 3, 9, and 20 mg/h). An additional cohort received a 5-day continuous infusion of 15 mg/h co-administered with aspirin 325 mg daily.[52] BMS-962212 reached peak concentrations 1-2 hours after dose administration, which corresponded to the maximal effect on the aPTT and sustained for the duration of the infusion.[51] The half-life ranged from approximately 2-5 hours in the single infusion arms and 6.2-8.6 hours in the continuous infusion arms. As such, the aPTT normalized approximately 4-12 hours postinfusion. Trends in aPTT were consistent with the observed trends in FXI activity with mean FXI decrease of 2.3%, 20%, 46%, 73%, and 83% in the placebo, 1.5, 4, 10, and 25 mg/h single infusion dose groups compared to baseline. With regard to bleeding times, no was increase observed with BMS-962212 or in combination with aspirin.[52] Initially there was concern of a decrease in estimated glomerular filtration rate and noted serum creatinine elevation (median increase 0.35 mg/dL [range 0.1-0.5 mg/dL) in 5 of 6 participants receiving the 1.5 mg/h infusion.[51] This finding was not noted any other dosing arm and further investigation revealed this transient elevation did not correspond with a true reduction in glomerular filtration rate. Overall, adverse events with BMS-962212 were mild, and generally limited to infusion-site reactions.

Lastly, JNJ-70033093 (BMS-986177) has completed study in health patients (NCT02608970) without published results.[53] Trials are also in the enrollment phase for active treatment in patients with acute ischemic stroke or transient ischemic attack in addition to aspirin and clopidogrel (AXIOMATIC-SSP; NCT03766581) and in patients undergoing elective total knee replacement compared to enoxaparin (AXIOMATIC-TKR; NCT03891524).[54,55]

CONCLUSION

Despite widespread use of NOACs for their clinical advantages, bleeding concerns remain and are associated with significant morbidity and mortality.[5-7] A focus on the development of therapeutics that target FXI have provided hope by observations in patients with FXI deficiency.[8] Monoclonal antibodies, ASO, and small molecule inhibitors of FXI have

exhibited success in preliminary studies on laboratory parameters, and animal studies on bleeding and thrombosis.

The phase II results of both FXI-ASO total knee arthroplasty and FOXTROT trials are encouraging for the development of anticoagulants that maximize safety.[43,48] They provide proof that inhibition of FXI can prevent venous thromboembolism following orthopedic surgery similar to accepted standards of care, and without increased risk of bleeding. While these agents demonstrated noninferiority compared to enoxaparin, the preoperative regimen of osocimab 1.8 mg/kg was found to be superior for VTE prevention.[43,48] However, relative increases in bleeding with the larger dose of osocimab may limit its pursuit in phase III studies.[48] Similarly, the 300-mg dosing regimen of IONIS-FXI was also superior to enoxaparin for VTE prevention, however the findings are limited by small sample size.[43] The dosing of IONIS-FXI and osocimab provide both advantages and disadvantages to future real-world applicability and other thrombotic indications. The frequent administrations of IONIS-FXI and necessity to begin treatment long before clinical efficacy (ie, prior to surgery) may limit the use for acute thrombosis; however, this may be advantageous for indications such as atrial fibrillation, where long-term treatment and fewer administrations might be favored over conventional therapy. Reversal in the setting of acute bleeding may be problematic with the prolonged half-life of these drug classes without a specific reversal agent, although replenishing factors with activated prothrombin complex concentrates or recombinant factor VII may be possible.[56]

The addition of FXI inhibitors to the anticoagulant market has the potential to increase safety for patients who may not have been previously good candidates for anticoagulation or struggle with compliance. FXI inhibitors represent the next step as we continue our quest for the 'perfect' anticoagulant.

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