Review Article

Novel Anticoagulants Affecting Factors IX, XI, and XII

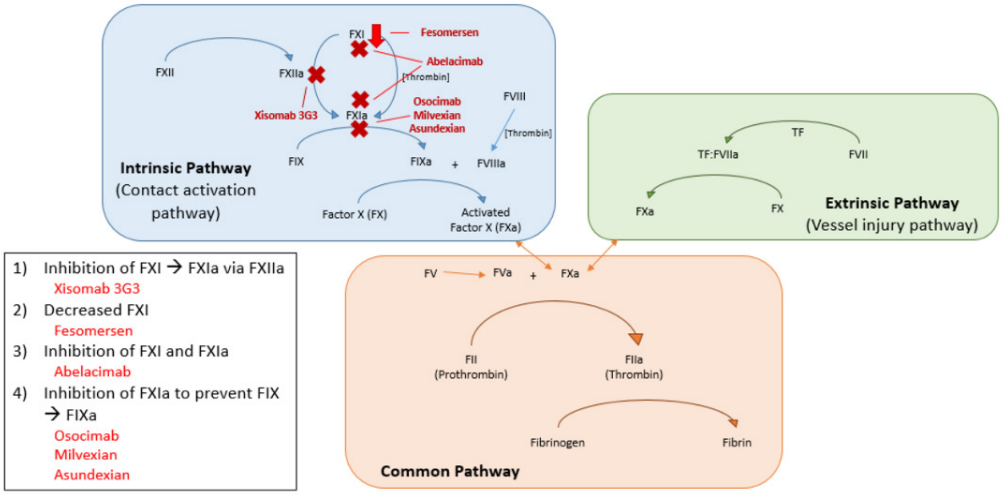
by Kaitlin Bruden, PharmD

When an elderly patient develops atrial fibrillation (Afib) and desires to be placed on anticoagulation, clinicians must think about which agent would be best. It is often difficult to determine a good anticoagulation regimen for patients with a high risk of bleeding; one of the biggest adverse effects of anticoagulation is the risk of bleeding. Some patients decide not to start anticoagulation due to this risk.[1,2]

One thing that unites all anticoagulants currently on the market is that they have an increased risk of bleeding. These agents have differing risks of bleeding (i.e. apixaban has been proven to have lower risk of bleeding than warfarin), but all have certain limitations when it comes to bleeding.[1] Direct acting oral anticoagulants (DOACs) have an estimated rate of major bleeding around 2-4% per year, while warfarin has a rate estimated to be ~0.4-7.2% per year.[3,4] Additionally, DOACs have limitations when it comes to their indications. For example, they have not been shown to be safe and effective for use in patients with antiphospholipid syndrome or mechanical heart valves.[2] These limitations have led to an unmet need for better anticoagulants.

All currently approved anticoagulants work in the same part of the coagulation cascade: the extrinsic pathway. At its simplest, there are three main parts of the coagulation cascade: the intrinsic pathway, the extrinsic pathway, and the common pathway.[5] The intrinsic pathway, also called the contact activation pathway, is more involved with inflammation and innate immunity, as well as being involved with coagulation once activated through the extrinsic pathway via thrombin.[2,5] The extrinsic pathway is considered the "initial spark" for coagulation and is involved with physiological hemostasis.[2] This pathway generates thrombin, which then goes on to involve the intrinsic pathway via factor XI (fXI) as can been seen in Figure 1;

FIGURE 1. Coagulation Cascade Depiction with Novel Agent Mechanisms, Adapted From Nopp et al[2]



thrombin also continues the clotting process in the common pathway.[1] FXI can also be activated by factor XIIa (fXIIa), a step higher in the intrinsic pathway.[6]

Factor XII (fXII) and fXI have gained interest as targets for novel anticoagulants. The major advantage is the hypothesis that these factors will target and decrease the risk of thrombosis while having minimal increased risk of bleeding.[2] What makes these targets different from those of the currently approved agents on the market is that fXI/fXIa and fXII/fXIIa reside within the intrinsic pathway of the coagulation cascade. Recent research seems to support that the intrinsic pathway is involved with pathologic thrombosis, so by inhibiting this pathway, there would be a lower thrombotic risk while leaving physiological hemostasis unchanged.[2,7] There have been discussions about which factor would be a better target.[6] Considerations include that fXI can be activated even without fXII via thrombin and the extrinsic pathway and that fXII-independent processes have been shown to be more significant for thrombosis in some studies. FXI deficiency is a known disorder called hemophilia C; from looking at data on patients with hemophilia C, we know these patients have a mild bleeding disorder–they have a decreased risk of thrombotic events and a low risk of non-trauma related bleeding.[2,5,6,8] Less is known about fXII deficiency than fXI deficiency; current epidemiological data show patients with fXII deficiency are not at lower risk of venous thromboembolism (VTE), stroke, or myocardial infarction (MI) and may actually have a higher risk of thrombotic events.[1]

Discussion

There are many novel agents in Phase II and III studies. These agents have different formulations, so they could have slightly different uses or dosing intervals; for example, monoclonal antibodies are often infused, while small molecule drugs could be an oral option. How the drugs elicit their intended effects can also vary–some agents block the active site of the intended factor while others silence the gene expression of the factor of interest.[2] The differences in mechanisms could also differentiate the agents as we learn more about the intrinsic pathway and the processes involved with thrombosis. The population for which each agent is studied will also affect initial uses. Agents that have been studied in patients undergoing knee replacement include fesomersen (formerly IONIS-FXIRX or

ISIS-416858), osocimab, abelacimab, and milvexian. Many of these novel agents are being researched in patients with end-stage renal disease (ESRD) or patients who are on hemodialysis, which is a population often excluded from clinical trials.

Agents Targeting FXI

Fesomersen is an fXI-directed antisense oligonucleotide (ASO) agent that decreases the amount of fXI and its activity levels with concentration-dependent properties. A phase II study with patients undergoing elective knee replacement compared fesomersen 200 or 300 mg per week, subcutaneously, starting 35 days prior to surgery, with enoxaparin 40 mg daily starting after surgery. Mean fXI levels were reduced to 38% and 28% of baseline values in those receiving the 200 and 300 mg. The 200 mg fesomersen regimen was non-inferior and the 300 mg ASO regimen was superior to enoxaparin for the primary efficacy outcome of VTE. All groups had similar rates of bleeding. This agent has also been looked at in trials of patients with ESRD.[1]

Agents Targeting FXIa

Agents with this mechanism prevent fXIa from activating fIX. Osocimab is a monoclonal antibody that binds to and inhibits FXIa, preventing this from activating FIX. It is a monthly subcutaneous injection or intravenous infusion that has been studied in knee replacement so far with a single intravenous dose given pre- or post-operatively. When compared to enoxaparin 40 mg daily and apixaban 2.5 mg BID, osocimab 0.6 mg/kg post-op, 1.2 mg/kg post-op, and 1.8 mg/kg post-op doses met the criteria for noninferiority compared to enoxaparin while osocimab 1.8 mg/kg pre-op also met the criteria for superiority compared to enoxaparin for VTE rates. Osocimab showed lower bleed rates than enoxaparin in all groups.[9] There is a study with osocimab in patients with ESRD underway that uses a monthly subcutaneous formulation.[1] The two different formulations of osocimab have different doses and frequency recommendations, which makes this agent different from other novel medications mentioned in this article. Milvexian is a small molecule that inhibits fXIa. This is a daily or twice-daily oral medication and has been studied in knee replacement with an upcoming study looking at its effects in ischemic stroke. Seven dosing regimens of milvexian were compared to enoxaparin; four dosing regimens were superior to enoxaparin with all groups having similar bleeding and adverse events.[1,10] Asundexian is a small molecule inhibitor of fXIa; it is a daily, oral option that has been studied in atrial fibrillation. It has no significant drug interactions with CYP3A4, giving it an advantage over the current DOAC agents. Two doses of asundexian were compared to apixaban and showed lower bleed rates than apixaban. There were cases of ischemic stroke in both asundexian arms and none in the apixaban group, showing more efficacy data is needed in Phase III trials.[1,11] There is a completed and ongoing Phase II study in patients with recent myocardial infarction and non-cardioembolic stroke, respectively.[1]

Agents Targeting FXI and FXIa

Abelacimab is another monoclonal antibody; it works by binding to and inhibiting both fXI and fXIa. In a study comparing intravenous doses to enoxaparin in patients undergoing knee replacement, all 3 doses (30-mg, 75-mg, 150-mg) of

TABLE 1. Drug Information for Novel Agents Targeting FXI (fesomersen)

	Fesomersen
Mechanism	FXI-directed antisense oligonucleotide (ASO) agent
Rationale	Decreases amount of FXI and its activity in a concentration-dependent manner
Formulation	Subcutaneous injection
Dosages studied	100 mg per week 200 mg per week* 300 mg per week‡ *Patients received 9 doses over 39 days with first dose 36 days prior to surgery*
Comparator	Enoxaparin 40 mg daily subcutaneous
Population studied	Elective knee replacement (VTE prophylaxis)
Safety	Similar bleeding with comparator
Future studies	Patients with ESRD

*: non-inferior to comparator; ‡: superior to comparator

TABLE 2. Drug Information for Novel Agents targeting FXIa (osocimab, milvexian, and asundexian)

	Osocimab	Milvexian	Asundexian
Mechanism	Monoclonal antibody that binds and inhibits FXIa	Small molecule that inhibits FXIa	small molecule inhibitor of FXIa
Rationale	Prevents activation of FIX	Prevents activation of FIX	Prevents activation of FIX
Formulation	Monthly subcutaneous injection or intravenous infusion	daily or twice-daily oral medication	daily, oral option
Dosages studied	0.3 mg/kg pre-op 0.3 mg/kg post-op 0.6 mg/kg post-op* (enoxaparin) 1.2 mg/kg post-op* (enoxaparin) 1.8 mg/kg post-op* (enoxaparin) 1.8 mg/kg pre-op‡ *All doses given as a single, 60-minute, intravenous infusion*	25 mg BID 50 mg BID‡ 100 mg BID‡ 200 mg BID‡ 25 mg once daily 50 mg once daily 200 mg once daily‡	20 mg once daily 50 mg once daily
Comparator	enoxaparin 40 mg daily and apixaban 2.5 mg BID	Enoxaparin 40 mg daily	Apixaban 5 mg BID
Population studied	Elective knee replacement (VTE prophylaxis)	Elective knee replacement (VTE prophylaxis)	Atrial fibrillation with moderate-high risk of stroke and bleeding
Safety	lower bleed rates than enoxaparin in all groups	All doses similar bleeding and adverse events	Lower bleed rates than apixaban
Future studies	Patients with ESRD on HD (monthly subcutaneous injection)	Ischemic stroke prevention	More efficacy studies needed (in atrial fibrillation)

*: non-inferior to enoxaparin; ‡: superior to enoxaparin

abelacimab showed non-inferiority to enoxaparin 40 mg with superiority met for the 75-mg and 150-mg abelacimab regimens, and rates of bleeding were similar in all groups.[12] There are ongoing studies in atrial fibrillation (for safety outcomes) and cancer-related thrombosis.[1]

Agents acting as FXIIa inhibitors

Xisomab 3G3 is a monoclonal antibody that has been studied in ESRD. It binds to fXI and blocks its activation from fXIIa; fXI activation via thrombin is not inhibited, making this agent unique by acting like an fXIIa inhibitor. In the study of patients with ESRD who need heparin-free dialysis, no bleeding events related to the study drug occurred, and results for efficacy were promising but underpowered. Another study involving artificial surfaces is ongoing; this one is for prevention of catheter-related thrombosis in patients with cancer.[1]

Conclusion

There is a lot of potential from early Phase II and Phase III studies of these novel medications. What is still unknown with these agents is if their efficacy will be similar or better than current agents. It is also unknown if there will be off-target effects from these agents due to their novel mechanism of action.[5,6] While these agents seem to have an increased safety profile from these early studies, larger landmark trials will be needed to determine their safety and efficacy on a larger scale.[13] It is an exciting time to be in the field of anticoagulation, and we'll have to wait and see how the landscape shapes up in the next few years.

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TABLE 3. Drug Information for Novel Agents Targeting FXI and FXIa (abelacimab)

	Abelacimab
Mechanism	monoclonal antibody that binds to and inhibits both FXI and FXIa
Rationale	Prevents activation of FIX
Formulation	Single intravenous infusion
Dosages studied	Intravenous 30-mg abelacimab* Intravenous 75-mg abelacimab‡ Intravenous 150-mg abelacimab‡
Comparator	Enoxaparin 40 mg
Population studied	Elective knee replacement
Safety	Similar bleeding in all groups, none clinically relevant
Future studies	Atrial fibrillation (for safety); Cancer-related thrombosis

*: non-inferior to comparator; ‡: superior to comparator

TABLE 4. Drug information for novel agents targeting FXI conversion to FXIa via FXIIa (xisomab 3G3)

	Xisomab 3G3
Mechanism	monoclonal antibody that binds to FXI (acts like a FXIIa inhibitor)
Rationale	blocks FXI activation from FXIIa without affected FXI activation from thrombin
Formulation	0.25 mg/kg injected into dialysis line 0.5 mg/kg injected into dialysis line
Dosages studied	0.25 mg/kg injection 0.5 mg/kg injection
Comparator	Placebo
Population studied	patients with end-stage renal disease who need heparin-free dialysis
Safety	No bleeding related to study drug occurred
Future studies	Efficacy data needed in patients with end-stage renal disease who need heparin-free dialysis; artificial surfaces for prevention of catheter-related thrombosis in patients with cancer

*: non-inferior to comparator; ‡: superior to comparator