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Abelacimab: A leap forward in anticoagulation with FXI and FXIa Inhibition

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ABSTRACT

Direct Oral Anticoagulants (DOACs) have revolutionized the treatment of thromboembolic disorders, offering targeted, effective, and safer alternatives to traditional anticoagulants like heparins and vitamin K antagonists (VKAs). Despite their benefits, DOACs have drawbacks, including an increased risk of gastrointestinal bleeding and unsuitability for patients with mechanical heart valves. Recent research has highlighted Factor XI (FXI) as a promising anticoagulation target due to its significant role in pathological thrombosis and minor involvement in normal hemostasis. Abelacimab, an antibody that inhibits FXI, has shown potential in transforming anticoagulation therapy by sparing hemostasis. This review provides a comprehensive analysis of abelacimab, examining its clinical pharmacology and its pharmacokinetic and pharmacodynamic properties. It scrutinizes abelacimab's safety profile and key monitoring parameters. The current evidence supporting its use and potential future research strengthening its position in anticoagulant therapy is also discussed. The objective is to enhance understanding and contribute to discussions around developing safer anticoagulants, particularly for patients at risk for thrombosis.

1. Introduction

For more than 50 years, warfarin, among the vitamin K antagonist class, remained the primary anticoagulant agent prescribed for prophylaxis and treatment of VTE, as well as protecting patients with increased risk of stroke (Sikorska and Uprichard, 2017). They target the vitamin K epoxide reductase complex (VKROC1), which effectively inhibits the activation of vitamin K in the body (Sikorska and Uprichard, 2017). The variation in anticoagulant response, the limited therapeutic range requiring frequent monitoring of the international normalization ratio (INR), and the risk of severe bleeding are considered a significant limitation of warfarin.

Direct Oral Anticoagulants (DOACs) represent a significant advancement in the treatment of thromboembolic diseases (Franchini et al., 2016; Chen et al., 2020). Developed due to the limitations of traditional anticoagulants, DOACs directly inhibit specific proteins in the coagulation cascade, offering a more targeted approach to anticoagulation. DOACs, including dabigatran, rivaroxaban, apixaban, and edoxaban, have proven to be at least as effective as VKAs in preventing stroke in atrial fibrillation (AF) and managing venous thromboembolism (Chen et al., 2020). They offer numerous advantages over VKAs, such as less frequent monitoring and follow-up, a more immediate onset and offset of anticoagulant effect, and fewer drug and dietary interactions. These benefits make them a safe and effective alternative for many patients. However, DOACs have disadvantages. One significant concern is that they increase the risk of gastrointestinal bleeding compared to warfarin (Chen et al., 2020). Additionally, they are not recommended for patients with mechanical heart valves (Chen et al., 2020). Selecting the most suitable DOAC can also be challenging due to the availability of several different agents.

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As this field continues to evolve, Factor XI (FXI) is considered a promising target for the prevention of thromboembolism due to its significant role in pathological thrombosis yet minor involvement in normal hemostasis (Li T et al., 2022). This interest is driven by studies indicating that congenital FXI deficiency lowers the risk of venous thromboembolism (VTE) and stroke without increasing the risk of severe bleeding. Among various FXI-directed strategies, abelacimab has garnered significant attention (Santoro et al., 2015). This antibody, which inhibits FXI and its activated form FXIa, is being explored as an innovative solution in anticoagulation. Abelacimab has demonstrated the potential to transform our approach to anticoagulation by sparing hemostasis.

In this focused review, we delve into an intricate exploration of abelacimab, examining its clinical pharmacology and pharmacokinetic and pharmacodynamic properties. We scrutinize its safety profile, discussing critical parameters for monitoring its effects on patients. Furthermore, we assess the evidence supporting its use and consider prospective research that may further solidify its role in anticoagulant therapy. By providing a detailed analysis of abelacimab, we aim to enhance understanding of its potential role in patients requiring anticoagulation therapy. This review aims to add to the ongoing conversation regarding developing anticoagulants with superior safety profiles.

2. Clinical pharmacology

Factor XI (FXI) is the zymogen of a blood coagulation protease, factor XIa (FXIa), that contributes to hemostasis by activating factor IX. Factor XI is a precursor of an S1 serine protease found in blood plasma (Mohammed et al., 2018). When activated to FXIa, it plays a crucial role in forming and stabilizing fibrin by triggering the activation of factor IX. Factor XI is a 160-kDa protein composed of two identical chains with 607 amino acids. Every chain features four repeated sections, each with 90 or 91 amino acids, termed apple domains (from A1 to A4 starting at the N-terminus).

FXI directly activates the extrinsic pathway by interacting with various enzymatic substrates (Mohammed et al., 2018). Initially, FXI was believed to be exclusively a part of the "contact" pathway. However, it was later found that thrombin can also activate this factor, which is a part of the extrinsic pathway. The primary target for FXIa is the contact pathway factor FIX. Still, research has shown that FXI can activate FX in a lab setting (Fig. 1). Moreover, FXI aids in generating thrombin by activating cofactors FVIII and FV. FXIa is also recognized for its ability to reduce clotting time independently of FIX. Furthermore, FXIa boosts the activation of the extrinsic pathway by breaking down the tissue factor pathway inhibitor (TFPI), a specific kind of protease that halts the TF/FVIIa/FXa complex. The involvement of platelets is crucial for FXIa to effectively support hemostasis via the extrinsic pathway (Mohammed et al., 2018; Schmaier, 2014).

FXI deficiency is linked to a mild bleeding condition commonly referred to as hemophilia C. Unlike hemophilia A or B, FXI deficiency doesn't typically manifest in muscle or joint bleeds, severe internal cerebral hemorrhages, or gastrointestinal bleeds (Wheeler and Gailani, 2016). In contrast, epidemiological and animal studies data highlight FXI's role in thrombosis. People with FXI deficiency tend to have lower rates of venous thromboembolism (VTE) and ischemic strokes than the general population (Salomon et al., 2011). Conversely, individuals with elevated FXI levels have over double the VTE risk (Spiezia et al., 2023). In various animal models, reducing FXI or inhibiting its action decreased the incidence of thrombotic episodes post-injury. This data implies that FXI might be more crucial in thrombosis than general hemostasis. During a thrombotic event, thrombus formation is likely initiated by tissue factor (TF) found on modified vascular endothelium or present on leukocytes, extracellular microvesicles, or damaged endothelial cells. However, the ability of the FVIIa/TF complex to push forward thrombus growth might be restrained when the thrombus gets too big and surpasses the TF source located at the injured vessel's wall (Tillman and Gailani, 2018). It seems FXI plays a pivotal role in encouraging thrombus expansion. Thrombin stands as the primary FXI activator during thrombosis. Moreover, polyanions, possibly found in an expanding thrombus, such as chromatin pushed out from activated neutrophils (neutrophil extracellular traps) or inorganic polyphosphates released from excited platelets or microvesicles from red blood cells or stimulated platelets, can trigger FXII and bolster further FXI activation by FXIIa (Shi et al., 2021). Additionally, in cases where blood exposure to synthetic surfaces causes thrombosis (like during cardiopulmonary bypass, hemodialysis, or with central venous catheters), thrombin

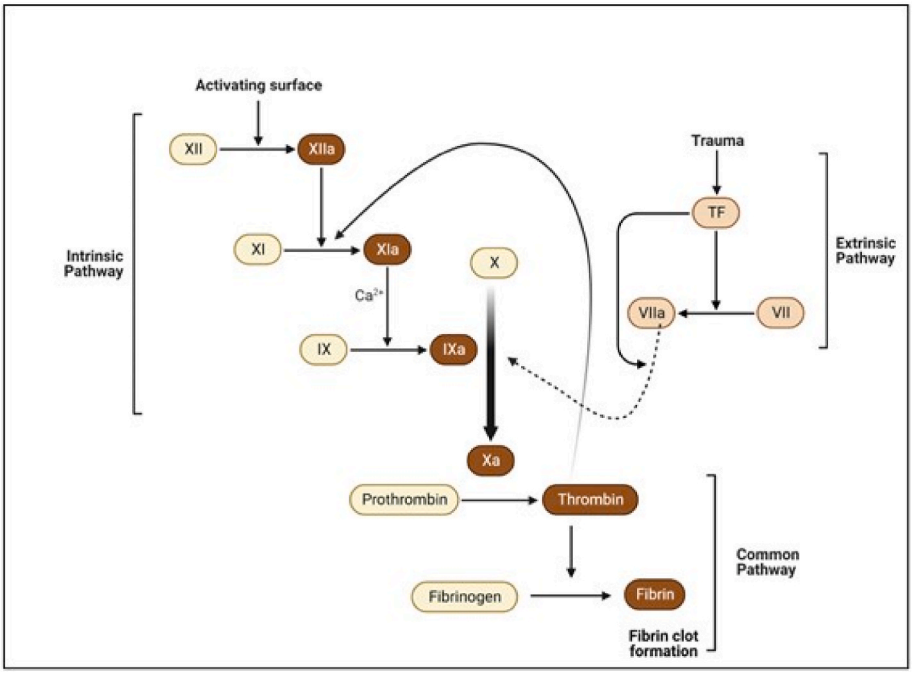

Fig. 1. Blood coagulation enzyme processes. This illustrates the cascade model for thrombin formation initiated by FXII activation.

creation might majorly start with FXIIa's activation of FXI, rather than the FVIIa/TF complex (Tillman and Gailani, 2018). Irrespective of the underlying mechanism of activation, FXI emerges as a pivotal target for regulating thrombin synthesis and thrombotic propagation.

The modern phase of pharmacology has led pharmaceutical companies to adopt strategies beyond the traditional small chemical compounds. These new approaches include the use of monoclonal antibodies (mAbs) and antisense oligonucleotides (ASO) to regulate the coagulation cascade. Abelacimab is a monoclonal antibody designed to bind and suppress both FXI and FXIa. The Fab segment of abelacimab showcases a strong binding affinity to FXI and FXIa, halting 50% of FXIa's activity at a concentration of 2.8 nM. Notably, this action is highly targeted, as it doesn't impact other human serine protease-type coagulation factors, like factor VIIa, IXa, Xa, FXIIa, thrombin, or its close counterpart, plasma kallikrein (Campello et al., 2022). Abelacimab has a marked affinity for the catalytic domain of human FXI and FXIa (Fig. 2). Insights from the X-ray structure of the Fab segment of abelacimab combined with the FXIa catalytic domain showed that the antibody secures and stabilizes the protease in an inactive form. Due to this action, abelacimab extends the clotting time, as gauged by the Activated Partial Thromboplastin Time (aPTT) test, and diminishes thrombin levels in human plasma based on concentration. Lab tests have highlighted that abelacimab hampers FXIa activated by FXIIa in the intrinsic pathway and thrombin. Yet, it doesn't affect the initial thrombin spike initiated by the extrinsic pathway. In essence, abelacimab halts the activation of circulating FXI and counters any preexisting FXIa (Campello et al., 2022).

3. Pharmacokinetic and pharmacodynamic

The pharmacokinetic profile of abelacimab has been evaluated in healthy volunteers. The time to peak plasma concentration was dose-independent, ranging from 1.75 to 2 h (Yi et al., 2022; Koch et al., 2019). This agent's half-life ($t_{1/2}$) of elimination ranges from 25 to 30 days. The immediate concentration following the injection (C_0) and the area under the curve (AUC) were reported to be reduced by up to 45% among obese subjects. The PK profile of abelacimab at different dose levels is summarized in Table 1.

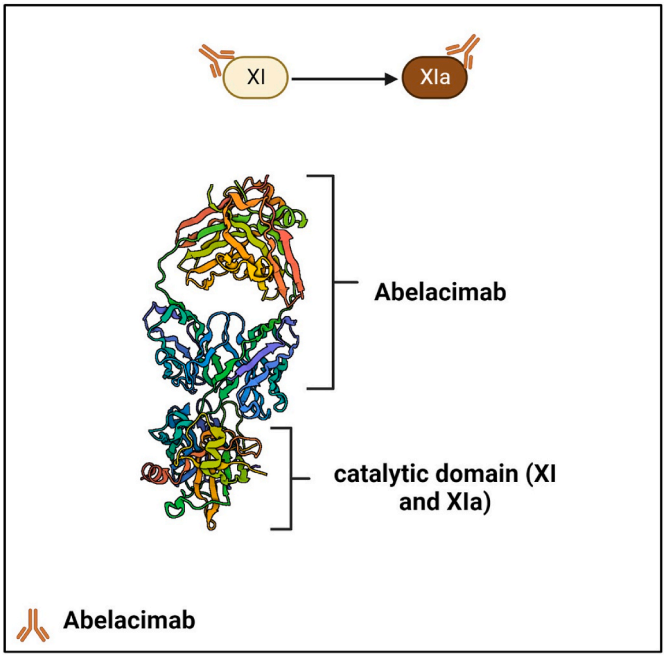

Fig. 2. Depiction of abelacimab's interaction with the catalytic domain of FXI and FXIa.

Table 1
Abelacimab pharmacokinetics profile at different doses.

PK parameters	C0 (μg/ml)	Cmax (μg/ml)	T1/2 (h)	AUC_{inf} ($h \times \mu g/ml$)	Vss (L)	CL (L/h)
Abelacimab 30 mg	7.50 (26.7)	9.43 (21.0)	621 (12.6)	2940 (34.2)	8.48 (32.1)	0.0102 (34.2)
Abelacimab 50 mg	10.8 (9.2)	12.2 (12.8)	709 (38.0)	4020 (20.3)	8.48 (32.1)	0.0124 (20.3)
Abelacimab 150 mg	44.2 (21.0)	52.3 (17.7)	595 (29.7)	22969 (17.6)	5.00 (24.1)	0.00653 (17.6)
Abelacimab 150 mg in obese patients	31.0 (13.7)	36.7 (16.8)	621 (17.1)	12543 (26.6)	8.29 (20.8)	0.0120 (26.6)

C0: initial concentration, **Cmax:** initial concentration, ***T1/2:*** terminal elimination half-life, ***AUC_{inf}***: area under plasma concentration-time curve from time 0 to infinity, **Vss:** steady state volume of distribution, **CL:** clearance, **PK:** pharmacokinetics.

4. Pharmacodynamics

Abelacimab intravenous infusion (IV) has resulted in a 99% rapid reduction of factor XI concentrations at doses of 30 mg, 50 mg, and 150 mg. Recovery of factor XI level was dose-dependent; the earliest FXI activity was seen around day 10 with the 30 mg dose (Koch et al., 2019). The activated partial thromboplastin time (aPTT) ratio was doubled by hour 1 post IV infusion across all doses and went back to baseline in a dose-dependent manner (Verhamme et al., 2021). Similarly, abelacimab subcutaneous injection (SubQ) led to a sustained reduction of factor XI over approximately 11 days before reaching its nadir, and FXI levels returned to baseline before the next monthly dose was due with monthly SubQ injections. The doubling of aPTT ratio was detected with SubQ injections, and elevation in aPTT was sustained in correlation with abelacimab's serum concentration (Yi et al., 2022; Verhamme et al., 2021).

5. Safety profile

The safety profile of abelacimab was evaluated in a phase II trial comparing IV abelacimab at doses of 30 mg, 75 mg, and 150 mg to the standard of care (enoxaparin) for the prevention of VTE. One clinically significant bleeding event was reported in a patient who received abelacimab 75 mg and ended up developing hemarthrosis and undergoing surgery on day 12 post-infusion. Three other bleeding events were classified as non-major with abelacimab 30 mg and 75 mg; notably, no bleeding events were reported in the 150 mg group (Verhamme et al., 2021). Other randomized controlled trials reported no bleeding events with abelacimab (Yi et al., 2022). Abelacimab IV and SubQ were well tolerated, with no hypersensitivity events reported across different dosing ranges (Yi et al., 2022; Verhamme et al., 2021). Data from phase III trials will further help shape the understanding of abelacimab's safety profile (Table 2).

6. Clinical studies

Abelacimab (MAA868) is still not FDA-approved; however, clinical studies have showcased its potential, promising efficacy, and safety. The initial phase I clinical trial, conducted with a progressive single dosage, showed that a subcutaneous dose ranging from 5 to 240 mg/kg was safe and efficacious in healthy and obese individuals (Koch et al., 2019). Notably, at a dose of 150 mg/kg, the activated partial thromboplastin time (aPTT) was extended for a minimum of four weeks. This was observed without notable impact on the prothrombin time (PT) and thrombin time. Additionally, the effects of MAA868 were reversed by recombinant activated factor VII. It was further observed that either intravenous administration or multiple subcutaneous dosages were also

Table 2
Summary of ongoing abelacimab trials.

Trial Name: Design and Population	Intervention Arm	Control Arm	Key Measured Outcomes	ClinicalTrials.gov Identifier
AZALEA-TIMI 71 Trial: Phase II study in patients with atrial fibrillation	Abelacimab	Rivaroxaban	Rate of major or clinically relevant non-major bleeding events, major bleeding	NCT04755283
LILAC-TIMI 76 Trial: phase 3 study in high-risk patients with atrial fibrillation unsuitable for oral anticoagulation therapy	Abelacimab	Placebo	Rate of ischemic stroke or systemic embolism in patients with atrial fibrillation	NCT05712200
ASTER Trial: phase 3 study in Cancer patients	Abelacimab	Apixaban	VTE recurrence, and major or clinically relevant non-major bleeding	NCT05171049
MAGNOLIA Trial: phase 3 study in patients with gastrointestinal/ genitourinary cancer	Abelacimab	Dalteparin	VTE recurrence, and major or clinically relevant non-major bleeding	NCT05171075

deemed safe for patients diagnosed with atrial fibrillation (Yi et al., 2022).

One major trial, the ANT-005 TKA trial, has been at the forefront of these discussions (Verhamme et al., 2021). The ANT-005 TKA trial was a phase 2, open-label study focused on patients undergoing total knee arthroplasty. A total of 412 Pa were randomly assigned to receive varying doses of abelacimab (30 mg, 75 mg, or 150 mg) post-surgery or a daily dose of enoxaparin. The primary goal was the occurrence of venous thromboembolism (VTE), with a secondary focus on major or clinically relevant non-major bleeding up to a month post-operation. While 22% of patients on enoxaparin experienced VTE, the incidence of VTE was reduced to 13%, 5%, and 4% for the 30-mg, 75-mg, and 150-mg abelacimab groups, respectively. Notably, the two higher dosages of abelacimab showcased superior efficacy compared to enoxaparin. The safety outcomes were similarly encouraging, with minimal bleeding incidents across the board. In the abelacimab groups, 2% of patients from both the 30-mg and 75-mg categories experienced bleeding, while none from the 150-mg group did. Similarly, no patients in the enoxaparin group reported bleeding.

The AZALEA-TIMI 71 trial is another phase 2 study, which had to be halted prematurely due to the markedly positive results in reducing bleeding in patients on abelacimab compared to those on rivaroxaban (Ruff, 2013). This trial involved 1287 atrial fibrillation patients at a moderate-to-high stroke risk. Patients were randomized 1:1:1 and abelacimab 150 mg once monthly, abelacimab 90 mg once monthly, or rivaroxaban 20 mg daily. The findings from this promising research have yet to be published. Given its impressive results in reducing both bleeding and thrombosis, abelacimab is poised to revolutionize anticoagulant therapy.

7. Future studies

Table 2 provides a concise overview of abelacimab ongoing studies. These studies aim to offer a clearer understanding of the application of abelacimab in various patient groups. Specifically, the TIMI trials focus on patients with atrial fibrillation, while the ASTER and MAGNOLIA trials explore its use in patients with cancer-associated VTE.

8. Conclusions

While awaiting FDA approval, abelacimab stands out as a promising anticoagulant agent. Nonetheless, more data may be needed to establish its efficacy and safety in the prevention and management of VTE in special populations, such as patients with cancer or hepatic and renal insufficiency and elderly patients. Lastly, further investigation is needed to validate the antagonists of FXI inhibitors, their combination with other drugs, and monitoring parameters.

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Hisham A. Badreldin: Conceptualization, Methodology, Project administration. **Nada Alsuhebany:** Writing – original draft, Writing – review & editing. **Mohammed Alzahrani:** Writing – original draft. **Abdulmajeed M. Alshehri:** Writing – original draft. **Maha Aldoughaim:** Writing – original draft. **Saleh Alqifari:** Writing – original draft. **Omar Yassin:** Writing – original draft. **Lama Alfehaid:** Supervision, Writing – review & editing. **Tariq Alqahtani:** Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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