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The new in anticoagulation: factor XI inhibitors

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Haemostasis and thrombosis are closely linked, so that any anticoagulant strategy available today that reduces the thrombotic risk inevitably increases the bleeding risk. However, epidemiological and experimental evidence suggests that inhibiting the contact pathway—the first phase of the intrinsic coagulation pathway—and especially factor XI (FXI) achieves the objective of preventing thrombosis with minimal interference on the haemostatic process. Several pharmacological strategies that act by inhibiting FXI are being studied in clinical trials. Specifically, Phase 2 clinical trials in patients undergoing major orthopaedic surgery, end-stage renal disease, atrial fibrillation (AF), and acute coronary syndrome have shown promising results, allowing clinical research to advance into Phase 3 clinical trials. FXI inhibitors will not necessarily replace currently available direct oral anticoagulants: this would appear too ambitious as of today. However, it is possible to hypothesize that FXI inhibitors are a useful addition to our therapeutic armamentarium in contexts where current anticoagulants have failed or have not been adequately tested, as well as in categories of patients who are at a high risk of bleeding even with current direct oral anticoagulants.

Introduction

Direct oral anticoagulants (DOACs) are currently the most widely used anticoagulants in the Western world. The predictable pharmacokinetics, the ease of use, and the wide therapeutic window, as well as the overall favourable profile efficacy and/or safety profile, are undoubtedly the most important advantages over older oral anticoagulants. Both in the prevention of stroke in patients with AF and in the prevention and treatment of venous thromboembolism (VTE), DOACs have demonstrated efficacy at least similar to heparin and vitamin K antagonists (VKA), with less incidence of intracranial haemorrhage and lesser mortality. In addition, low dose rivaroxaban combined with antiplatelet therapy has been shown to reduce the incidence of major adverse cardiovascular events and mortality in patients with a recent acute coronary syndrome, stable coronary artery disease, and peripheral arterial disease. However, there are categories of patients in whom the DOACs have failed to demonstrate a favourable efficacy/safety profile, or are contraindicated, or have not been adequately tested. This is the case, first of all, in patients with mechanical prosthetic heart valves or in subjects suffering from a triple-positive antiphospholipid antibody syndrome, where DOACs have proved to be inferior in efficacy to VKAs. Direct oral anticoagulants have not been adequately tested in patients with impaired liver function, severe renal insufficiency, or very high glomerular filtration rate, as well as in individuals with extremes of body weight. This is also the case in patients in whom the blood is exposed to artificial surfaces, such as mechanical assistance to the circulation or extracorporeal membrane oxygenators: in these cases, data on the use of DOACs compared with VKAs are lacking. Furthermore, even today, in patients with a high bleeding risk the decision to start or continue anticoagulant treatment remains mostly discretionary, based on an individual assessment of thrombotic and bleeding risk. Specifically, the risk–benefit ratio of oral anticoagulants in patients on dialysis or cancer is still debated. Furthermore, DOACs increase the risk of gastrointestinal bleeding compared with VKAs. Therefore, in such settings a safer anticoagulant strategy could represent an important new treatment option.[1]

Why inhibiting FXI? The premises and the rationale

Modern coagulation theories hypothesize that it is possible to distinguish, at least in part, the mechanism of

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pathological thrombosis from that of physiological haemostasis.[2] Currently available oral anticoagulants all interfere with factors X/Xa and II/IIa, which belong to the common pathway of coagulation and which are therefore essential also in the processes of physiological haemostasis.[3] The knowledge derived from some genetic disorders and in numerous experimental animal models have rekindled the interest in the contact phase of the intrinsic coagulation pathway, highlighting its substantial role more in processes of pathological thrombosis than in those of physiological haemostasis. The hypothesis of developing anticoagulants with a better safety profile that possibly attain the Holy Grail of preventive thrombosis dissociating it from physiological haemostasis certainly derives from the knowledge of some genetic disorders. In particular, people with congenital factor XI (FXI) deficiency, also known as haemophilia C or Rosenthal disease, have decreased levels and activity of coagulation FXI. These patients have a lower risk of thrombotic events, albeit with minimal bleeding tendency.[4] Haemophilia C is transmitted by incomplete autosomal recessive inheritance, affecting equally males and females. The prevalence of homozygous FXI deficiency is one case per million people, although a higher frequency has been reported in the Jewish population, reaching 8–9% among Ashkenazy Jews.[5] Bleeding episodes here are modest and rarely spontaneous. Bleeding essentially appears only following traumatic events, tooth extractions, surgery, or postpartum. Women may have menorrhagia. Against this minimal bleeding tendency, coagulation tests are markedly impaired. Indeed, FXI deficiency prolongs the activated partial thromboplastin time (aPTT), which monitors the intrinsic coagulation pathway, without altering the prothrombin time (PT), a measure instead of the extrinsic pathway.[1] This modest bleeding tendency suggests that FXI plays a mostly secondary and minor role in the processes of haemostasis. Contrary to this, many evidences have now shown that activation of FXI is crucial in atherothrombotic phenomena.[6] Furthermore, subjects with high levels of FXI have a risk of deep vein thrombosis (DVT) 2.2 times higher than subjects with normal levels.[7] Studies conducted on experimental animal models also support the predominant role of FXI in thrombotic phenomena, with minimal influence on haemostasis. Specifically, mouse models deficient in FXI show normal bleeding after tail amputation, with a lower tendency to thrombus formation at sites of artero-venous injury.[8] Similarly, in these experimental models the use of antibodies directed against FXI reduces the incidence of thrombosis.[9] In experimental models in baboons, treatment with anti-FXI monoclonal antibodies reduces the deposition of platelets and fibrin at sites of vascular grafts without altering the bleeding time, while the use of antibodies directed against factor XII (FXII) is less effective in this sense.[8]

Haemostasis-thrombosis uncoupling

Considering haemostasis and thrombosis processes totally dependent on the same enzymatic reactions is a simplistic approximation. In fact, various evidences confirm to date the hypothesis that haemostasis is mainly dependent on the extrinsic pathway of coagulation, while the intrinsic pathway is more involved in the pathological growth of the thrombus. Researchers have therefore focused on inhibition of the intrinsic pathway, and FXI has appeared as the most promising candidate target. FXII (or activated FXII, FXIIa), also belonging to the intrinsic coagulation pathway, has so far proved to be less important: several epidemiological studies have in fact failed to demonstrate an association between FXII levels and risk of VTE, ischaemic stroke, or myocardial infarction.[10]

Haemostasis is the physiological response to a damage to the vessel wall. It is primarily an extra-vascular process, and is triggered by the exposure of blood to high concentrations of tissue factor (TF) present in the adventitia of blood vessels, which occurs after injury to the vessel wall. High concentrations of TF bind FVII converting it to activated FVII (FVIIa), and the FVIIa:TF complex converts FX to FXa, which is responsible for the initial, limited production of thrombin from prothrombin. This initial production of thrombin leads to the formation of fibrin, and this, together with FXa, acts, in a positive feedback, to activate key cofactors such as FV and FVIII. The limited amount of thrombin generated early leads to the formation of an unstable clot. In addition to activating FX, the FVIIa:TF complex converts FIX to FIXa. FIXa—with FVIIIa as a cofactor—maintains thrombin production through sustained FX activation, resulting in the formation of a stable clot.[2] The importance of this pathway in haemostasis is demonstrated by the occurrence of severe bleeding secondary to hereditary FVIII and FIX deficiencies, known as haemophilia A and B, respectively.[11] However, the ability of the FVII:TF complex to promote thrombus growth within the vessel lumen may be limited by the expansion of the thrombus beyond the site of vascular damage, i.e. exposure of TF.[2]

The contact system, high in the intrinsic coagulation pathway, has been scarcely considered for many years because the physiological activators of this pathway were not well known, and the congenital deficiencies of its factors such as FXII, high molecular weight kininogen (HMWK) and prekallikrein (PK) were not associated with bleeding. Furthermore, congenital FXI deficiency was responsible, as mentioned above, for only a minimal bleeding diathesis. Therefore, the activation of the contact system was mostly seen as a phenomenon of little importance *in vivo*, in practice an *in vitro*, laboratory phenomenon, occurring after contact of the blood with negatively charged surfaces. However, studies conducted in the past 15 years have identified several potential physiological activators, with increasing evidence confirming the predominant role of the intrinsic pathway in thrombus expansion and stabilization. Activators include various polyanions, such as nucleic acids released from activated cells and strands of nuclear material expelled from activated neutrophils (neutrophil extracellular traps, NETs), as well as polyphosphates released from activated platelets and microorganisms. These activators are therefore mainly observed at sites of inflammation and infection, following phenomena of cell activation and apoptosis. In the presence of polyanions, for example, FXII is self-activated, and converts FXI into FXIa. This in turn activates FIX to FIXa, in turn responsible for the activation of FX, thus converging in the common pathway of coagulation with the eventual production of thrombin and fibrin.[10]

Why would FXI inhibitors have the potential to reduce ‘pathological’ thrombosis with no or minimal interference on the haemostatic phase? Thrombosis is triggered by low concentrations of TF exposed at rupture sites of atherosclerotic

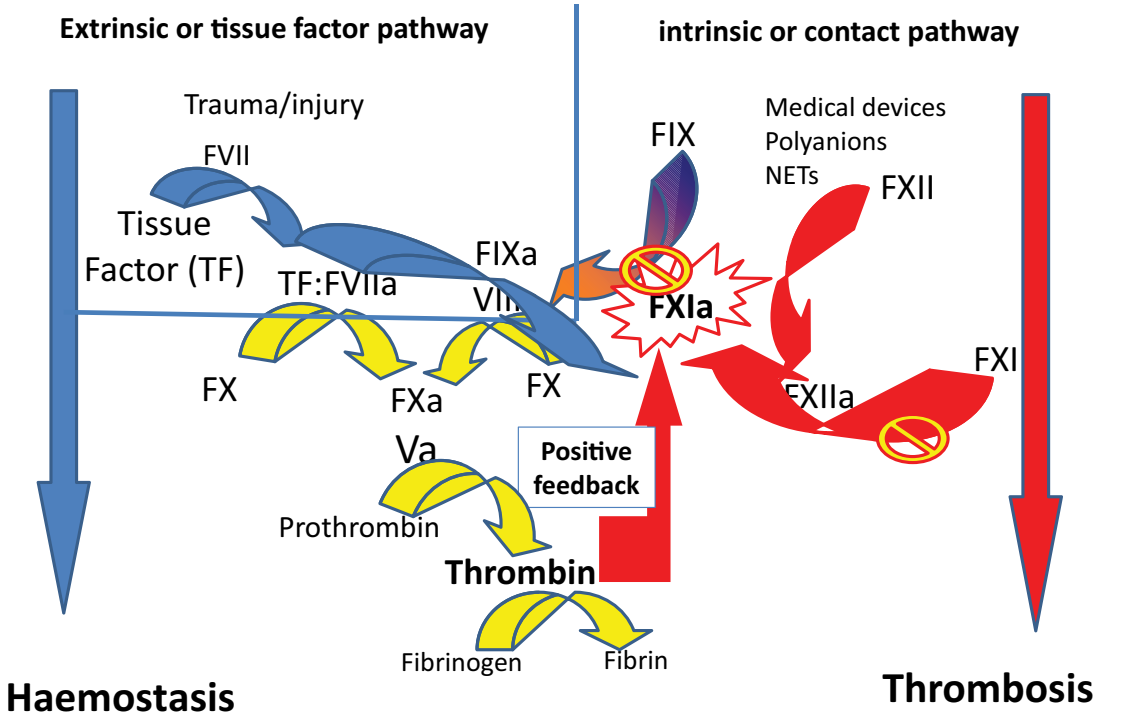

Figure 1 The possible dissociation between haemostasis and thrombosis. Haemostasis is triggered by the exposure of tissue factor (TF) in the adventitia of blood vessels and tissues after vascular injury. High concentrations of TF, through the extrinsic pathway of coagulation, lead to the production of thrombin and the formation of the haemostatic plug. Specifically, high concentrations of TF bind FVII converting it to activated FVII (FVIIa), and the FVIIa:TF complex converts FX to FXa, which in turn is responsible for an initial and limited production of thrombin from prothrombin. This initial thrombin production leads to fibrin formation and, together with FXa, acts in a positive feedback loop to activate key proteins, such as FV and FVIII. In addition to activating FX, the FVIIa:TF complex converts FIX to FIXa. FIXa, which has FVIIIa as a cofactor, maintains thrombin production through a sustained activation of FX, resulting in stable clot formation. FXII and FXI are not strictly necessary for the formation of a stable clot. The intrinsic pathway of coagulation is, instead, triggered by lower concentrations of TF present at rupture sites of atherosclerotic plaques, as well as by various polyanions, neutrophil extracellular traps (NETs), and medical devices in contact with circulating blood. In the presence of these activators, FXII self-activates and converts FXI into FXIa, which in turn activates FIX. FIXa is responsible for the activation of FX by converging in the common pathway of coagulation, with production of thrombin and fibrin. The central role of FXI/FXIa derives from a specific positive feedback mechanism that takes place between thrombin and FXI/FXIa, leading to an exponential increase in the production of thrombin and fibrin with 'uncontrolled' expansion of the thrombus, hence the rationale to inhibit FXI/FXIa to block pathological thrombosis while preserving physiological haemostasis as much as possible. Left side arrows: extrinsic coagulation pathway; right side arrows: intrinsic coagulation pathway; central arrows: common coagulation pathway.

plaques, as well as on the activated endothelium that binds activated monocytes and microvesicles. This thrombotic process, in addition to physiological polyanions, can be triggered by contact with the artificial surfaces of medical devices that bind FXII and promote its self-activation. In this case, the activation of FXI leads to the production of thrombin, which in turn, through a positive feedback mechanism, retroactivates FXI, thus amplifying the formation of thrombin and fibrin and leading to thrombus expansion. Thus, it is the positive feedback between FXIa and thrombin that is primarily responsible for pathological thrombosis. With minimal or no activation of FXII and little or no positive feedback between FXI and thrombin, the extrinsic pathway appears self-sufficient for the formation of a haemostatic plug. In fact, this is achieved even in the presence of very low levels of FXI, even when reduced to 10–20%. Hence the rationale to inhibit the FXI to block 'pathological' thrombosis with no or minimal interference on the haemostatic phase. Targeting the contact phase also appears reasonable in cases where thrombosis is secondary to blood contact with artificial surfaces of medical devices, such as haemodialysis circuits, catheters, and mechanical heart valves[1,2] (*Figure 1*).

FXI inhibitors in development

Starting from these pathophysiological premises, drugs have been developed that are able to inhibit FXI or FXIa.[12] These can be classified into three main categories on the basis of their chemical structure, namely:

(1) Antisense oligonucleotides (ASOs): these reduce the hepatic synthesis of FXI (IONIS-FXI$_{Rx}$ and fesomersen)
(2) Monoclonal antibodies (mAbs): these bind to FXI or FXIa and block their activation or activity (osocimab, abelacimab, xisomab 3G3, and MK-2060)
(3) Small molecules: these reversibly bind FXIa, blocking its activity (milvexian, asundexian, and EP-7041)

Natural inhibitors and aptamers against FXI are still in pre-clinical development and not yet tested in humans.

Different pharmacokinetic and pharmacodynamic properties characterize the aforementioned classes, and this entails advantages and disadvantages specific to each category. ASOs act by reducing the synthesis and therefore the levels of FXI, unlike the other drug categories which

bind, thereby inhibiting, the target protein (FXI or FXIa). Only the small molecules can be administered orally. They have a rapid onset of action, but also a short half-life, so that their administration is once or twice a day. ASOs take 3–4 weeks to reduce FXI levels, whereas monoclonal antibodies have a rapid onset of action, especially when given intravenously rather than subcutaneously. ASOs and monoclonal antibodies also have a long half-life, which allows for monthly dosing. Unlike small molecules, ASOs and monoclonal antibodies are not excreted by the kidney, and interactions with other drugs are unlikely, since they are not metabolized by cytochrome P450 and are not a P-glycoprotein substrate. In addition, mAbs can be immunogenic and induce injection site autoimmune reactions. ASOs, conversely, can exert pro-inflammatory effects and induce nephrotoxicity, hepatotoxicity, and thrombocytopenia. All this can be reflected in potentially different therapeutic indications, as well as in a different safety profile.[1]

Potential clinical applications

Several FXI inhibitors have to date successfully completed Phase 2 clinical trials in patients undergoing major orthopaedic surgery, patients with AF, and patients with end-stage renal disease. Overall, the four inhibitors evaluated in the prevention and treatment of VTE secondary to major orthopaedic surgery have demonstrated at least non-inferiority to low molecular weight heparins, but with a better safety profile. Factor XI in the prevention of thromboembolic events in subjects suffering from AF and in those with end-stage renal disease or on haemodialysis has shown reassuring results in terms of safety, pharmacodynamics, and pharmacokinetics, although not yet with sufficient efficacy data. Nevertheless, they have provided solid foundations for research progressing to Phase 3 clinical trials. Phase 2 clinical trials are ongoing to evaluate the efficacy and safety of FXI inhibitors for prevention of VTE in cancer patients, known to have a high bleeding risk. In this clinical context, in fact, DOACs, although effective, have here shown a non-negligible risk of bleeding. Pre-clinical data also support the notion that reductions in FXIIa or FXIa are associated with a lower risk of catheter-related thrombosis. In this regard, a Phase 2 clinical study is evaluating the prevention of thrombosis from central venous catheters (CVC) in cancer patients undergoing chemotherapy. A further avenue of research is that of secondary cardiovascular prevention after a myocardial infarction and of thrombo-prophylaxis in patients affected by COVID-19.[1]

Conclusions

What is expected of FXI inhibitors? These drugs will have to face a tough battle in which the main objective will be to satisfy the needs still unmet by the current DOACs and carve out a niche for themselves within the wide range of possible therapeutic options for anticoagulation. This means that, at least initially, the goal will not be to replace current DOACs, but provide drugs in those clinical settings in which DOACs are contraindicated or in which their usefulness has not been fully established. In this regard, the most important indications may be the prevention of major adverse cardiovascular events in patients with end-stage renal disease or haemodialysis, and the prevention of thrombosis from medical devices such as central venous catheters, mechanical valve prostheses, and ventricular assist devices. Finally, an equally effective treatment strategy, but with a better safety profile, will be particularly useful in clinical contexts with a higher bleeding risk, such as cancer patients or those with AF who are candidates to a double or triple therapy, as well as in the secondary prevention of patients with a previous myocardial infarction.[13] A more ambitious goal is to replace DOACs for at least equal efficacy but better safety in AF. Other indications could be acute coronary syndromes and ischaemic stroke, in which there is still no consensus on the use of oral anticoagulants at the present time. Ongoing or planned Phase 3 clinical studies will have to provide all the necessary evidence regarding the efficacy and safety profiles of this new therapeutic strategy and its potential use in the various hypothesized clinical contexts.

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Data availability

No new data were generated or analysed in support of this research.

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