Milvexian and other drugs targeting Factor XI: a new era of anticoagulation?

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For almost 90 years, the discovery and development of anticoagulant drugs have focused on maximizing their antithrombotic efficacy while minimizing the risk of bleeding, in addition to providing manageable compounds with predictable and/or monitorable effects. Nowadays, clinicians can rely on a large equipment of anticoagulants, going from the first discovered unfractionated heparin to the latest approved direct oral anticoagulants, passing through vitamin K antagonists, low molecular weight heparin/fondaparinux and parenteral anti-thrombin agents.

Nonetheless, in clinical scenarios requiring long-term or indefinite anticoagulation, such as stroke prevention in atrial fibrillation (AF) or secondary prevention of venous thromboembolism (VTE), and/or in comorbid and fragile patients, there is still an underuse of anticoagulants and an inappropriate use of dose reductions,[1,2] that are mainly driven by concerns about the risk of bleeding.

Therefore, over the last few years, research efforts have focused on a new class of anticoagulants targeting the contact system, with the aim to maximize safety by reducing the risk of bleeding while on therapy. Factor XI appeared to be an ideal target, because of its important role in thrombus growth, that is associated with a concomitant marginal role in hemostasis.[3]

A number of different molecules targeting Factor XI have been developed and a wide research program is currently ongoing. These molecules include antisense oligonucleotides (ASO) that inhibit the hepatic synthesis as well as agents that bind the target protein, such as monoclonal antibodies, small molecules and natural inhibitors.[4]

Phase II clinical trials carried out in patients undergoing elective major orthopedic surgery have been completed and published for fesomersen (IONIS-FXI-Rx)[5] and the antibodies osocimab and abelacimab.[6,7] More recently, a phase II randomized clinical trial tested the use of the small molecule milvexian, a selective oral Factor XIa inhibitor, for the prevention of VTE after total knee replacement (TKR).[8] Milvexian was given postoperatively in seven parallel groups at different doses and schedules. The results confirmed a significant dose-response relationship for both once daily and twice daily regimens. Moreover, the primary outcome (composite of asymptomatic deep vein thrombosis and symptomatic VTE) occurred in a significantly lower proportion of patients receiving milvexian at a total daily dose of 100 to 400 mg, as compared to enoxaparin. Overall, no episodes of major bleeding were registered with milvexian and clinically relevant bleeding (composite of major bleeding and clinically relevant non major bleeding) occurred in 1% of patients on milvexian and 2% of patients on enoxaparin. Of note, no dose-response relationship was seen for milvexian with respect to bleeding.[8]

This lower risk of clinically relevant bleeding was also observed in the first published phase II trial comparing fesomersen to enoxaparin, even if the difference did not reach statistical significance (3% *versus* 8%, respectively).[5] Of note, fesomersen inhibits hepatic biosynthesis of Factor XI and is therefore characterized by a very slow onset (and offset) of action, thus requiring to be started five weeks before surgery.

A good safety profile also resulted with the two monoclonal antibodies, osocimab, a fully human immunoglobulin G that binds the catalytic domain of FXIa and blocks its activity, and abelacimab, that binds to factor XI and locks it in the zymogen (inactive precursor) conformation. Osocimab met the non-inferiority criteria when

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administered at a single intravenous post-operative dose of 0.6, 1.2 or 1.8 mg/kg compared with enoxaparin for the prevention of VTE after elective TKR. Clinically relevant bleeding occurred in 4.7% of patients treated with osocimab 0.6 or 1.2 mg/kg and 5.9% with enoxaparin.[6] Similarly, abelacimab dose regimens of 30 mg and 75 mg/150 mg showed either non-inferiority or superiority, respectively, when compared to enoxaparin in preventing VTE after elective TKR. Clinically relevant bleeding occurred in 2%, 2%, and none of the patients in the 30-mg, 75-mg, and 150-mg groups, respectively, and in none of the patients in the enoxaparin group.[7]

The potential benefits of drugs targeting Factor XI may apply to several different clinical settings, in particular when the risk-benefit of anticoagulation is often uncertain. A number of studies are currently ongoing for the primary prevention of stroke in atrial fibrillation and the early secondary prevention of non-cardioembolic stroke (abelacimab, asundexian, milvexian), acute myocardial infarction (asundexian), and cancer-associated venous thromboembolism (abelacimab).[4] Another area of particular interest involves patients with end stage renal disease undergoing hemodialysis. These patients have repeated blood exposure to artificial surfaces that can activate the coagulation system within the hemodialysis circuit. Fesomersen, osocimab, milvexian, and xisomab have been evaluated in pilot studies aimed to understand the pharmacokinetics and pharmacodynamics of these drugs in such a particular group of patients and to evaluate their ability to prevent occlusive events requiring hemodialysis circuit exchange.[9]

In conclusion, a new era of research on anticoagulants targeting Factor XI has already started, with preliminary encouraging results on their efficacy and, importantly, on a trend towards a better safety profile. Even if the discovery of the "magic bullet" is going to remain utopia for quite a long time, in the next few years clinicians may hopefully be offered a new class of anticoagulant drugs, possibly applicable in different areas of vascular medicine.

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