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Weekly Journal Scan

Abelacimab and factor XI inhibition: a novel mechanism for the prevention of venous thromboembolism

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The results of 'Abelacimab for Prevention of Venous Thromboembolism' have been published in *N Engl J Med*. https://doi.org/10.1056/NEJMoa2105872.

Key Points

- This industry-promoted, phase-2, randomized, parallel-group trial compared the efficacy and safety of abelacimab, a fully human monoclonal antibody against factor XI (FXI), with enoxaparin in 412 patients undergoing elective, unilateral total knee arthroplasty (TKA). Patients (mean age, 67 years; 81% female) were randomly assigned in a 1:1:1:1 ratio to receive one of three regimens of abelacimab (30, 75, or 150 mg in a single intravenous infusion, 5 h after surgery) or enoxaparin 40 mg administered subcutaneously once daily (starting either the evening before or 12 hours after surgery) for a median of 9 days. Assignment to enoxaparin or abelacimab was open label, whereas assignment to an abelacimab regimen was blinded.
- Adjudicated venous thromboembolism (VTE) was the primary efficacy outcome. VTE was defined as a composite of asymptomatic deep-vein thrombosis (DVT; detected by mandatory unilateral venography performed between day 8 and day 12 after surgery), confirmed symptomatic VTE (symptomatic DVT of the leg or nonfatal pulmonary embolism (PE)], fatal PE, or unexplained death for which PE could not be ruled out. Adjudicated clinically relevant bleeding, a composite of major or clinically relevant nonmajor bleeding up to 30 days after surgery, was the principal safety outcome.
- VTE occurred in 4%, 5%, and 13% of patients in the 150-, 75-, and 30-mg abelacimab groups, respectively, compared with 22% of patients in the enoxaparin group. All three abelacimab regimens met the primary criterion for noninferiority to enoxaparin. The 75- and 150-mg regimens were both superior to enoxaparin ($P < 0.001$). Clinically relevant bleeding occurred in 2 of 102 patients (2%) assigned to receive abelacimab 30 mg, 2 of 104 (2%) patients assigned to receive 75 mg, none of 99 patients in the 150-mg group, and none of 104 patients in the enoxaparin group. Serious adverse events occurred during the trial in 1%, 3% and 1% of the patients in the 30-, 75-, and 150-mg abelacimab groups, respectively, and in none of the patients in the enoxaparin group.
- FXI activity and free FXI levels were inversely correlated with plasma concentrations of abelacimab, which increased in a dose-dependent fashion and declined slowly over 110 days.

Comment

FXI, a relatively novel target for thromboprophylaxis, appears to play a major role in pathological thrombosis, with limited role in physiological haemostasis.[2,3] Recent evidence suggests that inhibiting factors of the contact system, such as FXI and its activated form (FXIa), may effectively prevent pathological thrombosis without increasing bleeding risk.[1–3] Particular interest in the contact system of coagulation comes from epidemiological studies showing that patients with congenital FXI deficiency are at lower risk for VTE and stroke, but not at increased risk of serious bleeding.[4] In addition, studies in animals with antibodies directed against FXI and antisense oligonucleotide blocking FXI biosynthesis demonstrated that these agents may reduce thrombosis.[5] FXI-directed strategies include inhibitors of biosynthesis, antibodies (such as abelacimab), small molecules, and derivatives of naturally occurring inhibitors.[6–8]

In this phase-2 dose-finding trial, abelacimab was compared with enoxaparin in a low-risk population of patients undergoing elective TKA.[1] It should be emphasized that, in this setting, symptomatic DVT and PE rates are low, with a large contribution to postoperative thrombotic events by asymptomatic DVT.[9] Although these asymptomatic thrombi are of questionable clinical relevance, their venographic detection serves as a surrogate endpoint of the antithrombotic efficacy of new anticoagulants relative to that of a standard

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comparator.[6] In fact, 41 of 44 events of the primary outcome in the present study were represented by asymptomatic distal DVT, mostly limited to <2 veins.[1] The finding of superiority of the 75- and 150-mg abelacimab doses over enoxaparin in reducing the incidence of VTE is consistent with the fact that abelacimab inhibits the activation of FXI by both FXIIa and thrombin and supports the importance of FXI in thrombus growth and stabilization.[6]

In a phase-2 trial with a similar design involving 300 patients undergoing elective unilateral TKA, the higher dose (300 mg) of FXI-ASO, an antisense oligonucleotide that specifically reduces FXI levels, was more effective than enoxaparin in reducing venography-assessed VTE.[7] The finding that both abelacimab and FXI-ASO were shown superior to enoxaparin for the prevention of postoperative VTE reinforces the causal relationship between a largely suppressed FXI level and reduced incidence of postoperative venous thrombosis. However, while FXI-ASO had to be initiated 36 days before surgery to induce the knockdown of FXI to therapeutic levels, the intravenous infusion of abelacimab reduced the functional FXI level within minutes and for an extended time-frame, thereby enabling single postoperative dosing. Whether a persistent anticoagulant effect of abelacimab may represent a bleeding liability remains unanswered by the present study but should be carefully monitored during further clinical development.

Although the incidence of adjudicated clinically relevant bleeding was similarly low in both trials,[1,7] their small sample size and limited statistical power preclude reliable assessment of the haemostatic safety of these novel approaches.

Most direct FXa inhibitors are more effective than enoxaparin in preventing VTE after total hip or knee replacement, and their superior efficacy was not necessarily compromised by a higher bleeding risk.[10] All current anticoagulant drugs impact physiological haemostasis as well as pathological thrombosis, and previous attempts to spare the former while improving protection against the latter have largely failed.[6]

There is a biologically plausible expectation that FXI inhibitors may be effective in the prevention of VTE (and, possibly, other forms of thrombosis) without a comparable increase in bleeding risk, particularly in patients with end-stage renal disease, as antibodies and antisense oligonucleotides are not renally excreted.[6] However, verification of this hypothesis requires adequately sized phase-3 trials designed to assess the clinical efficacy and safety of FXI-directed approaches to thrombosis prevention.

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References

1. Verhamme P, Alexander Yi B, Segers A, Salter J, Bloomfield D, Buller HR, Raskob GE, Weitz JI. Abelacimab for prevention of venous thromboembolism. *N Engl J Med* 2021;**385**:609–617.
2. Zhang H, Löwenberg EC, Crosby JR, MacLeod RA, Zhao C, Gao D, Black C, Revenko SA, Meijers JCM, Stroes ES, Levi M, Monia BP. Inhibition of the intrinsic coagulation pathway factor XI by antisense oligonucleotides: a novel antithrombotic strategy with lowered bleeding risk. *Blood* 2010;**116**:4684–4692.
3. Weitz JI, Fredenburgh JC. 2017 scientific sessions sol sherry distinguished lecture in thrombosis: factor XI as a target for new anticoagulants. *Arterioscl Thromb Vasc Biol* 2018;**38**:304–310.
4. Preis M, Hirsch J, Kotler A, Zoabi A, Stein N, Rennert G, Saliba W. Factor XI deficiency is associated with lower risk for cardiovascular and venous thromboembolism events. *Blood* 2017;**129**:1210–1215.
5. Tillman BF, Gruber A, McCarty OJT, Gailani D. Plasma contact factors as therapeutic targets. *Blood Rev* 2018;**32**:433–448.
6. Fredenburgh JC, Weitz JI. Factor XI as a target for new anticoagulants. *Hämostaseologie* 2021;**41**:104–110.
7. Buller HR, Bethune C, Bhanot S, Gailani D, Monia BP, Raskob GE, Segers A, Verhamme P, Weitz JI. Factor XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med* 2015;**372**:232–240.
8. Koch AW, Schiering N, Melkko S, Ewert S, Salter J, Zhang Y, McCormack P, Yu J, Huang X, Chiu Y-H, Chen Z, Schleeger S, Horny G, DiPetrillo K, Muller L, Hein A, Villard F, Scharenberg M, Ramage P, Hassiepen U, Côté S, DeGagne J, Krantz C, Eder J, Stoll B, Kulmatycki K, Feldman DL, Hoffmann P, Basson CT, Frost RJA, Khder Y. MAA868, a novel FXI antibody with a unique binding mode, shows durable effects on markers of anticoagulation in humans. *Blood* 2019;**133**:1507–1516.
9. Januel JM, Chen G, Ruffieux C, Quan H, Douketis JD, Crowther MA, Colin C, Ghali WA, Burnand B; IMECCHI Group. Symptomatic in-hospital deep vein thrombosis and pulmonary embolism following hip and knee arthroplasty among patients receiving recommended prophylaxis: a systematic review. *JAMA* 2012;**307**:294–303.
10. Feng W, Wu K, Liu Z, Kong G, Deng Z, Chen S, Wu Y, Chen M, Liu S, Wang H. Oral direct factor Xa inhibitor versus enoxaparin for thromboprophylaxis after hip or knee arthroplasty: systemic review, traditional meta-analysis, dose-response meta-analysis and network meta-analysis. *Thromb Res* 2015;**136**:1133–1144.