FXI-ASO May Represent a New Class of Antithrombotic Agents

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Without prophylaxis, patients undergoing total knee arthroplasty (TKA) are at high risk for postoperative venous thromboembolism (VTE). Although traditional anticoagulants (eg, factor Xa or thrombin inhibitors) are effective, they are associated with a risk of bleeding. Patients with a severe factor XI (FXI) deficiency appear to have protection against deep vein thrombosis (DVT) [Salomon O et al. *Thromb Haemost*. 2011], and preclinical studies suggest that targeting FXI might reduce thrombosis without affecting hemostasis [Crosby JR et al. *Arterioscler Thromb Vasc Biol*. 2013; Zhang H et al. *Blood*. 2010]. Thus, FXI-directed agents are being investigated in clinical studies. One such agent is a second-generation single-stranded 2′-O-(2-methoxyethyl) antisense oligonucleotide to FXI (FXI-ASO).

Harry R. Büller, MD, Academic Medical Center, Amsterdam, Netherlands, presented the results of the Active Comparator-Controlled Study to Assess Safety and Efficacy of ISIS-FXIRx in Total Knee Arthroplasty [Büller HR et al. *N Engl J Med*. 2014]. This phase 2 open-label trial assessed the safety and efficacy of multiple subcutaneous doses of FXI-ASO in patients undergoing elective TKA.

Patients were randomly assigned 1:3 to enoxaparin, 40 mg, pre- or post-TKA for at least 8 consecutive days (n = 72) or to FXI-ASO, 200 mg (n = 144) or 300 mg (n = 77), on days 1, 3, 5, 8, 15, 22, and 29; 6 hours after TKA surgery (on day 36); and on day 39. Patients underwent bilateral venography on day 10 ± 2 post-TKA. Patients were followed to day 136.

The primary efficacy outcome was the composite of asymptomatic deep VTE detected by venography and confirmed symptomatic VTE. The secondary efficacy outcome included components of the primary efficacy outcome and the extent of VTE on venography. The primary safety outcome was a composite of major and clinically relevant nonmajor bleeding.

The demographics, clinical characteristics, and compliance with treatment were typical for patients undergoing TKA. About 80% were women with a mean age of 64 years. Treatment groups were well balanced for other factors, including mean FXI activity. Efficacy outcomes are shown in Table 1.

Both doses of FXI-ASO lowered FXI activity to a greater extent than enoxaparin, and more patients receiving the 300-mg dose of FXI-ASO had FXI levels ≤ 0.2 U/mL (59.2%) than did patients receiving the 200-mg dose (14.9%). The rates of VTE were lower in patients with FXI ≤ 0.2 U/mL that for those with FXI > 0.2 U/mL; the risk difference for FXI-ASO vs enoxaparin for patients with FXI ≤ 0.2 U/mL was –25.6% ($P < .001$); for those with FXI > 0.2 U/mL, there was no significant difference ($P = .42$).

The safety outcomes are shown in Table 2.

This study shows that FXI activity might play a role in the development of postoperative VTE and supports the concept that thrombosis and hemostasis can be dissociated. Reducing FXI levels using an ASO is an effective method for prevention of VTE and appears to be safe and well tolerated.

Table 1. Efficacy Outcomes

	Enoxaparin, 40 mg	FXI-ASO, 200 mg	FXI-ASO, 300 mg
Efficacy population	69	134	71
Total VTE	21 (30.4)	36 (26.9)	3 (4.2)
FXI-ASO vs enoxaparin[a]	N/A	–3.6 (5.1)[b]	–26.2 (–18.5)[c]
Components			
Symptomatic VTE	1 (1.4)	2 (1.5)	0
Asymptomatic DVT	20 (29.0)	34 (25.4)	3 (4.2)
Proximal DVT	4 (5.8)	7 (5.2)	1 (1.4)
Distal DVT	17 (24.6)	29 (21.6)	2 (2.8)

Values in No. (%), unless noted otherwise.

DVT, deep vein thrombosis; FXI-ASO, single-stranded 2′-O-(2-methoxyethyl) antisense oligonucleotide to factor XI; N/A, not applicable; VTE, venous thromboembolism.

[a]Risk difference (upper limit of 90% CI).

[b]$P = .59$.

[c]$P < .001$.

Table 2. Safety Outcomes, No.

	Enoxaparin, 40 mg	FXI-ASO, 200 mg	FXI-ASO, 300 mg
Safety population	72	144	77
Major bleeding	0	0	1
Clinically relevant nonmajor bleeding	6	4	1
Patients receiving blood transfusions	23	55	22

FXI-ASO, single-stranded 2′-O-(2-methoxyethyl) antisense oligonucleotide to factor XI.