The Effect of Increasing Factor X Levels on Emicizumab-Driven Coagulation Potential

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Thromb Haemost 2025;125:33–35.

Hemophilia A (HA) is a genetic bleeding disorder caused by a deficiency or defect in the factor VIII (FVIII) procoagulant protein. Regular use of FVIII products results in the development of anti-FVIII alloantibodies (inhibitors) in 20 to 30% of severe HA patients, increasing the risk of morbidity and mortality and complicating the management of these patients.[1] Until recently, the treatment options were limited to giving regular or as-needed bypassing agents, like recombinant activated factor VII (factor VIIa) or activated prothrombin complex concentrates, or inducing immune tolerance to eliminate FVIII inhibitors.[2] Currently, prophylaxis with emicizumab, a humanized bispecific antibody, is increasingly recognized as the standard of care for patients with HA, regardless of the presence of inhibitors. Emicizumab mimics FVIII cofactor activity by binding to activated factor IX and factor X (FX) to form a tenase complex that efficiently restores effective hemostasis.[3] In the recommended therapeutic concentrations, emicizumab significantly decreases bleeding events and corresponds to an FVIII activity level of 10 to 15 IU/dL assimilated to mild-phenotype hemophilia.[4] However, additional use of bypassing agents or FVIII is still necessary in patients receiving emicizumab in case of breakthrough bleeding or patients undergoing surgical procedures with high bleeding risk. In HA with inhibitors on emicizumab prophylaxis, the use of activated prothrombin complex concentrates was associated with thrombotic events, and the use of factor VIIa is recommended as the first-line treatment of bleeds.[5] Even if such adverse events were not reported with factor VIIa, the number of patients with HA with inhibitors treated for significant bleeding is limited until now; therefore, venous or arterial thrombotic events cannot be excluded. Moreover, recombinant factor VIIa should be administered frequently due to the short half-life of the product, making this therapy inconvenient; in certain situations, the bleeding does not stop after factor VIIa administration, and adding activated prothrombin complex concentrate is necessary, leading to an even higher risk of thrombotic complications.

It is essential to understand how to increase the hemostatic activity of emicizumab and to discover alternative methods for managing breakthrough bleeding in HA patients with inhibitors who are using emicizumab. In the latest issue of *Thrombosis and Haemostasis*, Shimizu et al offer additional insight into the impact of elevating FX levels on the coagulation potential in HA patients with inhibitors who are being treated with emicizumab.[6] The authors used in vivo and in vitro experiments. They evaluated global coagulation potential using the adjusted maximum coagulation velocity from clot waveform analysis, peak thrombin, endogenous thrombin potential from thrombin generation assay (TGA), and clotting time, clot formation time and α parameter from rotational thromboelastometry.[6]

In their in vitro experiments, the authors assessed the coagulation potential in FVIII-depleted plasmas and in plasma samples from patients with HA without inhibitors in which they added emicizumab (in a dose calculated to mimic the therapeutic concentration) and/or FX in increasing concentrations. When emicizumab alone was added to the FVIII-depleted plasma, the coagulation potential increased, and the supplemental addition of FX led to a more significant increase compared with baseline values. Adding FX only without emicizumab to FVIII-depleted plasma also led to an enhanced coagulation potential but of a lower magnitude than that obtained with emicizumab alone (►**Fig. 1A**). Interestingly, if the adjusted maximum coagulation velocity from

received
September 6, 2024
accepted
September 9, 2024
accepted manuscript online
September 11, 2024
article published online
October 1, 2024

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/a-2413-4453.
ISSN 0340-6245.

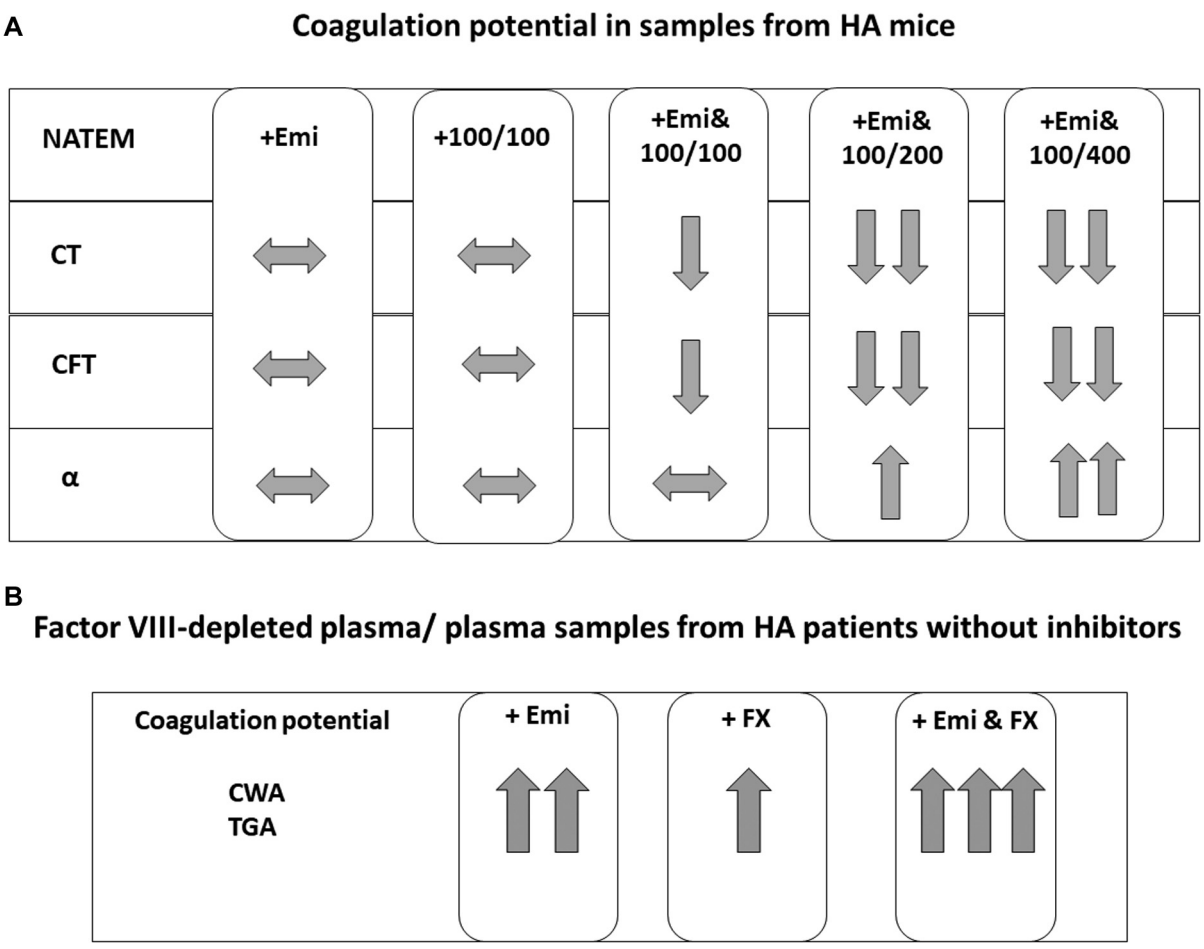

Fig. 1 (A) Coagulation potential in FVIII-depleted plasmas and plasma samples from hemophilia A (HA) patients after the addition of factor X and/or emicizumab. CWA, clot waveform assay; TGA, thrombin generation assay; +Emi, added emicizumab; +FX, added factor X; +Emi& FX, added emicizumab and factor X; the comparisons of coagulation potentials are made with raw plasma samples. (**B**) Coagulation potential in HA mice administered emicizumab and/or factors IX and X with factor X in increasing dosages. NATEM, nonactivated thromboelastometry; CT, clotting time; CFT, clot formation time; α, α angle; the comparisons of coagulation potentials are made with raw samples; +Emi, added emicizumab; +100/100, added human factor IX (100 IU/kg), and human factor X (100 IU/kg); +emi& 100/100, added emicizumab and human factor IX (100 IU/kg), and human factor X (100 IU/kg); +emi& 100/200, added emicizumab and human factor IX (100 IU/kg), and human factor X (200 IU/kg); +emi& 100/400, added emicizumab and human factor IX (100 IU/kg), and human factor X (100 IU/kg); the comparisons of coagulation potentials are made with raw samples.

clot waveform analysis and the peak thrombin from TGA increased dose-dependently with the amount of FX added to FVIII-depleted plasma with or without emicizumab, the other parameter recorded from TGA, endogenous thrombin potential, did not show the same tendency to increase in parallel with FX concentrations. In a second experiment, the authors demonstrated similar effects on the coagulation potential when factor VIIa and FX (in adjusted doses to obtain the concentrations attained in clinical use) were added to plasma samples from patients with HA with inhibitors treated with emicizumab.

In vivo, animal experiments used nonactivated rotational thromboelastometry to assess the hemostatic effects of increasing doses of FX in the presence of factor IX with or without emicizumab in HA mice. When only emicizumab or only coagulation factors were given, the coagulation parameters reflecting clotting initiation and propagation were not changed compared with untreated animals and improved only in animals treated simultaneously with emicizumab and coagulation factors (►**Fig. 1B**). Clinically, the hemostatic changes induced by increasing doses of FX in the presence of factor IX with or without added emicizumab were assessed by estimating the blood loss after a standardized tail clip in HA mice. The findings showed that the hemostatic effect of added coagulation factors was only visible in mice that received emicizumab as a decreased blood loss compared with untreated mice. At the same time, the differences in thrombotic markers measured in HA mice receiving emicizumab and mice receiving emicizumab plus additional FX were not significant.

Using in vitro and animal experiments, the authors have elegantly demonstrated that FX supplementation could enhance hemostatic mechanisms mediated by emicizumab in HA, with or without inhibitors. The combined use of FX and

emicizumab resulted in greater hemostatic effects than either alone. Importantly, the resulting global coagulation potential did not surpass the normal ranges, and the thrombotic risk was not enhanced even with high concentrations of FX.[6]

The results from Shimizu et al are consistent with those of Nakajima et al, who previously demonstrated improved hemostatic potential (but still lower than normal ranges) in FVIII-deficient plasma after adding emicizumab.[7] Improving hemostasis by using factor concentrates different from FVIII and factor IX, the missing factors responsible for hemophilias, is not new. Concentrates containing FX, or variants of FX capable of activating thrombin, were shown to increase coagulation potential in HA with or without inhibitors.[8–10] A recent article by Yada et al showed that the hemostatic response to factor VIIa in patients with HA with inhibitors was dependent on FX levels, being decreased with FX levels lower than 0.5 IU/mL.[11] However, in patients with HA with inhibitors treated with emicizumab, the coagulant response to factor VIIa was enhanced even at low FX levels.[11] The importance of FX levels in HA patients receiving emicizumab was also demonstrated by Kitazawa et al, who showed that more complexes are formed with emicizumab, factor IX/IXa, and FX/factor Xa when plasmatic FX levels are higher, leading to improved hemostatic potential.[12]

Currently, activated prothrombin complex concentrates and recombinant factor VIIa are recommended for breakthrough bleeding therapy in patients with HA treated with emicizumab. Considering the previous findings of increased thromboembolic risk with enhanced factor IX activity in emicizumab-treated patients,[13] using FX to increase hemostatic potential in HA patients would be preferable to using activated prothrombin complex concentrates. Another practical advantage is that, compared with factor VIIa, the half-life of FX is longer, with less frequent infusions needed. The study by Shimizu et al adds to the evidence in favor of exogenous FX therapy in combination with emicizumab for treating breakthrough bleeding in HA patients with inhibitors. Future research should focus on finding adequate therapy regimens using this approach.

Conflict of Interest
None declared.

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