SPOTLIGHT REVIEW ARTICLE

# Emicizumab: the hemophilia A game-changer

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## Abstract

In hemophilia, the unmet needs regarding adherence to prophylaxis and lack of effective long-term prophylaxis regimens, especially in patients with inhibitors, led to the production of emicizumab, the first non-factor medicine for subcutaneous administration in patients with severe and moderate hemophilia A with or without factor VIII inhibitors. This review describes the research steps behind the development of this game-changing medication as well as its success in the prophylaxis of bleeding episodes, as witnessed by the results of pivotal clinical trials but also by real-life use in the frame of a still expanding global market. We also discuss potential and actual adverse events and the nuances related to clinical use, such as laboratory monitoring, development of neutralizing antidrug antibodies, risk of thrombosis/hypercoagulability and role in the management of surgical operations. The potential of emicizumab to prevent bleeding in other congenital and acquired coagulation disorders is also outlined.

## Introduction

The history of hemophilia A (HA) treatment has been marked by solid innovation and progress, intended to improve the quality of life of individuals with this bleeding disorder. Emicizumab has contributed in a major way to this revolution as the first of the non-clotting factor options currently available to prevent hemorrhagic events in patients with congenital and acquired HA, with and without alloantibody inhibitors.

Prophylaxis strategies to prevent bleeding are considered the standard of care in HA.[1] The benefits of prophylaxis were confirmed by the sentinel randomized, prospective, multicenter trials by Lessinger *et al.* for patients with inhibitors and by Manco-Johnson *et al.* for inhibitor-free patients.[2,3] Both studies demonstrated that, compared to on-demand therapy, prophylaxis with infusions of anti-inhibitor complex bypassing activity concentrates, or of recombinant factor VIII (rFVIII), prevents joint damage and decreases the frequency of bleeding in joints and other sites in individuals with severe HA with or without inhibitors. The main impediments to success of such regimens have been adherence to the demands of predominantly twice weekly intravenous protocols for factor administration and the availability over time of functional venous accesses for the infusions. With the development and introduction of the recombinant, humanized, bispecific FVIII-mimetic procoagulant antibody, emicizumab, into the therapeutic armamentarium, the subcutaneous administration of hemostatic agents has improved adherence with equivalent safety and efficacy profiles compared to recombinant and plasma-derived concentrates for HA with or without inhibitors.

This review describes the history and pharmacology behind the development of emicizumab, the drug's initial success for prophylaxis against bleeds associated with alloantibodies neutralizing FVIII, its subsequent usefulness in prophylaxis regimens to prevent bleeds due to HA without inhibitors, and its potential use in other bleeding disorders. The review also discusses complications and the nuances associated with the use of emicizumab, such as laboratory monitoring, development of specific neutralizing antidrug antibodies, and thrombotic/hypercoagulability potential, and shows why this game-changing medication continues to capture an ever-expanding global market share among the hemostatic agents commercially available for the prevention of hemorrhagic episodes in subjects with HA.

## Development

The evolution of emicizumab as a therapeutic procoagulant reflects the convergence of intellectual insight

into the molecular mechanisms of thrombin generation mediated through activated factor VIII (FVIIIa) with the prowess of the pharmaceutical industry to innovate and bioengineer a molecular "linker". The concept of binding activated factor IX (FIXa) to factor X (FX) via a bispecific antibody to function as the FVIII cofactor was ascribed by Kitazawa and Shima to Dr. Kunihiro Hattori.[4] He and his research group at Chugai Pharmaceutical Co., Ltd. (Chugai) appreciated that the distance between the FIXa- and FX-binding sites of FVIIIa on a phospholipid template would be similar to that between the two antigen-binding sites of human IgG. Thus began the era of FVIII-mimetic therapy. Translating the concept of FVIII mimetics into a practical biopharmaceutical was a monumental and momentous task,[5-9] summarized in Figure 1.

## Dosing

Using population pharmacokinetic modeling and model-based simulations derived from phase I and II trials, the minimal emicizumab plasma concentrations expected to achieve zero bleeds over a 1-year period in at least 50% of patients were determined[10] and applied to formulate the dosing regimens employed in the pivotal phase III HAVEN trials: a subcutaneous loading dose of 3 mg/kg once weekly for a total of 4 weeks and three different subcutaneous maintenance doses starting at week 5: these doses were 1.5 mg/kg once every week, 3 mg/kg once every 2 weeks and 6 mg/kg once every 4 weeks. All regimens have shown comparable efficacy and similar side-effect profiles.

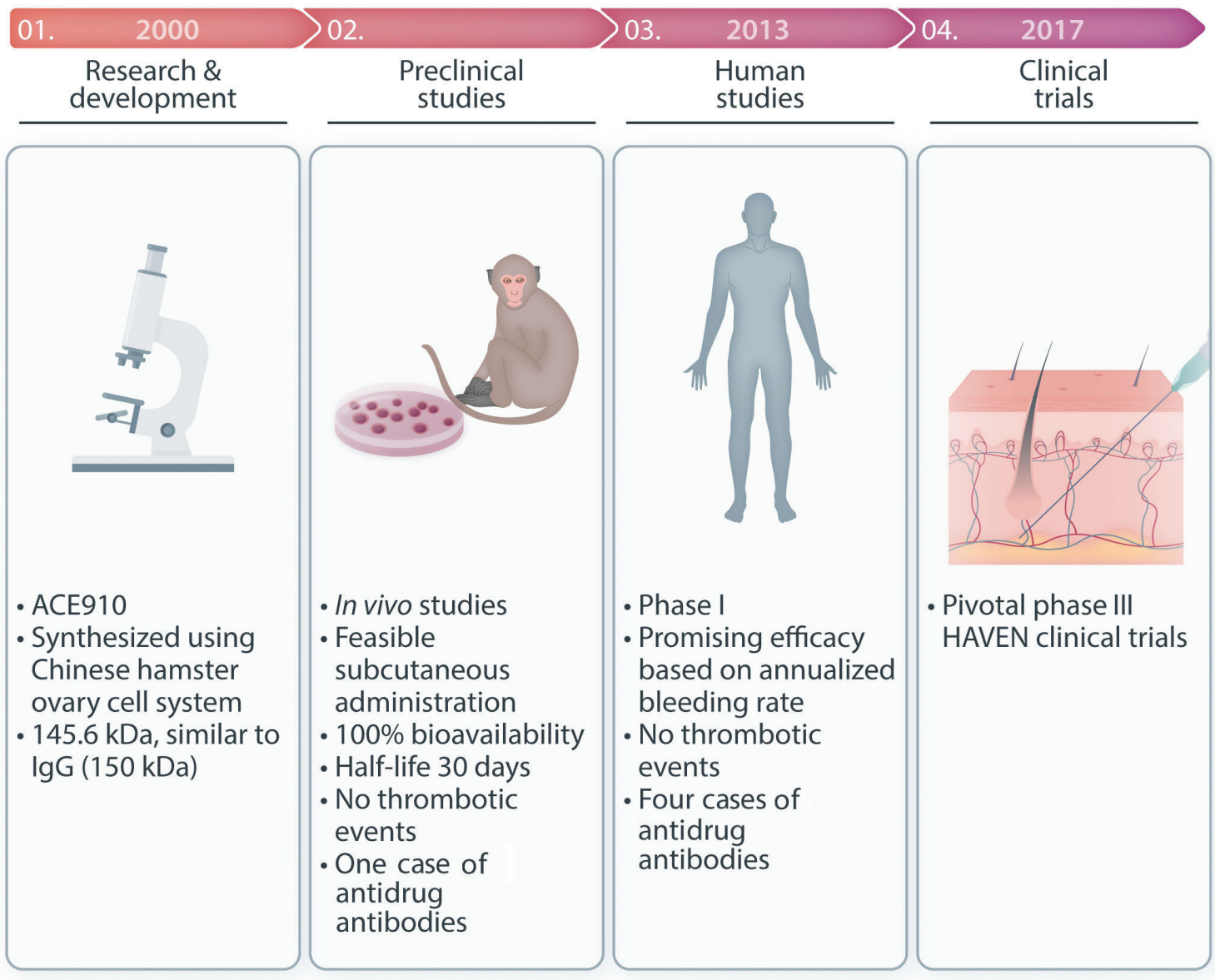


**Figure 1. Development of emicizumab.** Over 2,400 engineered monoclonal IgG molecules were tested and methodically modified and optimized to minimize non-specific binding and immunogenicity and to maximize physicochemical stability and their activated factor VIII-cofactor activity, leading to the development of ACE910, subsequently named emicizumab. *In vivo* studies were developed using primate models of acquired hemophilia A, in which bleeding events were successfully treated and prevented, and a once-weekly subcutaneous dosing provided the rationale for a prophylaxis protocol in people with hemophilia A. The first in-human study, started in 2013, was designed as a randomized and placebo-controlled, phase I trial using a single subcutaneous dose of emicizumab in healthy volunteers and demonstrated efficacy, high bioavailability from subcutaneous administration, without evidence of hypercoagulability. These findings were corroborated in short-term and long-term extension studies (12 weeks to 33.3 months, respectively) of weekly subcutaneous administration to patients with severe hemophilia A over 12 years old with or without inhibitors, which showed a decrease in annualized bleeding rate close to zero, regardless of the presence of inhibitors, and four cases of antidrug antibodies, which were non-neutralizing and did not cause changes in treatment.

## Pivotal clinical trials: establishing efficacy and safety

In the era of very effective FVIII replacement therapies resulting in a median annualized bleeding rate close to zero in most individuals with severe HA, the development of neutralizing anti-FVIII inhibitors has emerged as the highest priority complication of repeated exposure to FVIII products. This immune response to exogenous FVIII occurs in an estimated 20-40% of individuals with severe HA and 3-13% of those with mild-to-moderate HA,[11,12] and is associated with increased cost of care, mortality and morbidity, including a higher rate of bleeding, more disability and decreased quality of life.[13] Historically, the treatment and prevention of bleeding episodes in patients with FVIII inhibitors was achieved with administration of bypassing agents such as activated prothrombin complex concentrates (aPCC) and recombinant activated factor VII (rFVIIa). In practice, these products provided adequate hemostatic efficacy, although this was temporary and cumbersome to maintain, and less effective than FVIII replacement in patients without inhibitors.[14]

Thus, the promise of emicizumab as a convenient-to-administer, subcutaneous, non-factor FVIIIa mimetic with durable effectiveness was greatly anticipated when the HAVEN 1[15] and 2[16] clinical trials were launched. These phase III studies assessed the efficacy, safety, and pharmacokinetics of once-weekly subcutaneous emicizumab prophylaxis in patients with severe HA and FVIII inhibitors and led to the approval of emicizumab-kxwh by the US Food and Drug Administration (FDA) on November 16, 2017. Subsequent studies were designed to broaden the scope of emicizumab use, including patients without inhibitors (HAVEN 3 and 4),[17,18] patients of the Asia-Pacific region (HAVEN 5),[19] those with non-severe HA (HAVEN 6)[20] and infants (HAVEN 7).[21] Different dosing regimens were evaluated and showed the versatility of the drug. These results led to the US FDA and European Medicines Agency (EMA) approvals in 2018 of the multiple prescribing options for the use of emicizumab for prophylaxis in individuals with HA with or without FVIII inhibitors. Results are summarized in Table 1.

The positive results from these clinical trials, as well as the convenient dosing and administration regimens, have led to a rapid uptake for emicizumab in the international HA treatment marketplace. Since 2018, emicizumab is being used by over 12,500 patients[22] and generated $3.6 billion in sales in 2022 as the 34$^{th}$ best-selling pharmaceutical of 2022.[23] Its availability in developing nations is also well-established following distribution of 2,528,730 mg by the World Federation of Haemophilia to 806 patients in Africa, Latin America, Asia, and Eastern Europe. Of these individuals, 55% were under 12 years old and 64% were non-inhibitor patients.[22]

## Practical therapeutic concerns and questions

### Laboratory testing

As the use of emicizumab has increased, so too has the desire to have a routine laboratory assay available to monitor safety and efficacy. This would allow for individualization of dosing and lower costs. However, emicizumab interferes with clotting-based assays, while assays using immunological or chromogenic techniques are not affected[24,25] (Table 2).

Global coagulation testing techniques have been proposed to estimate the hemostatic potential of emicizumab. Thrombin generation assays and thromboelastography have been the most used platforms in this area.[26-28] Although these assays may reflect changes from baseline coagulation potential following emicizumab, they do not provide "true FVIII equivalence" *in vivo* and, in fact, a thrombin generation assay may overestimate thrombin levels in plasma specimens in the presence of emicizumab, since the assay is not modulated by the presence of naturally occurring circulating thrombin inhibitors, such as $\alpha_2$ macroglobulin.[28] Thus, thrombin-generation assays may lead to overconfidence and faulty clinical decision-making regarding the hemostatic response to emicizumab. It has been suggested that thrombin generation assays may be best used to limit the occurrence of adverse thromboembolic events when other procoagulant medications are administered to treat breakthrough bleeds in individuals on maintenance emicizumab regimens.[26] This was poignantly apparent in the HAVEN 1 study, in swhich five patients experienced thromboembolic events when emicizumab was combined with multiple high doses of aPCC. *In vitro* plasma spiking studies corroborated the marked synergistic effects on thrombin generation assays when aPCC was added to emicizumab.[29] However, despite suggestions that there is a direct correlation between the clinical bleeding phenotype of patients with hemophilia and their thrombin generation capacity, real-world experience with emicizumab has challenged this in sporadic clinical instances.[30]

Would measurement of emicizumab concentrations in plasma provide a more accurate FVIII equivalence? Extensive *in vitro* studies have not been able to establish true FVIII equivalence for emicizumab, probably due to the different modes of action to activate FX and to the vagaries in the methods of the biochemical assays.[28] Kitazawa *et al.* approached this issue by developing a primate bleeding model of acquired HA.[31] Using rFVIII as the FVIII calibrator, the therapeutic emicizumab level of about 55 μg/mL had an estimated FVIII equivalence activity level of 10-20%.[28] The HAVEN 1 study demonstrated a steady-state mean emicizumab level of 55 μg/mL (range, 35-70 μg/mL). Even though emicizumab assays are becoming more available commercially, it is anticipated that their use will be somewhat limited, perhaps to confirm a patient's adherence to prophylaxis and for confirmation of the presence of neutralizing anti-emicizumab antibodies.

## Adverse events associated with emicizumab administration

### Injection site reactions/hypersensitivity

Thus far, the administration of emicizumab has been remarkably routine and uneventful. Gelbenegger *et al.* summarized the adverse events recorded in all the HAVEN clinical trials.[32] The most frequently observed adverse events were local injection site reactions (erythema, pain, and pruritus), which were reported in 26.1% of treated participants. The reactions were mild to moderate in severity and resolved without treatment in over 90% of cases. Anaphylaxis was extremely rare. There were two adult cases of rhabdomyolysis, which occurred following intense physical exercise.

### Thromboembolic complications/thrombotic microangiopathy

The most concerning of the adverse events reported with emicizumab during clinical trials has been the occurrence of thromboembolic events and thrombotic microangiopathy, as summarized in Table 1. Critically, these complications were associated with concomitant replacement therapy with aPCC at cumulative doses over 100 U/kg/day for more than 1 day. An updated summary of thromboembolic events documented 37 additional cases of non-aPCC-related events

**Table 1.** Summary of results from the HAVEN clinical trials.

| Study | Population | Doses | ABR median (95% CI) | Zero bleed rate, N (%) | SAE | ADA | Ref |
|---|---|---|---|---|---|---|---|
| HAVEN 1 2017 | Adults and adolescents (≥12 years old) with inhibitors | 3 mg/kg QW x 4, followed by 1.5 mg/kg QW (N=35)<br>No prophylaxis (N=18) | 2.9* (1.7-5.0)<br>23.3 (12.3-43.9) | 22 (63)<br>1 (6) | 2 TMA<br>1 CST<br>1 superficial thrombophlebitis | None | 15 |
| HAVEN 2 2019 | Children (<12 years old) with inhibitors | 3 mg/kg QW x 4, followed by:<br>1.5 mg/kg QW (N=68)<br>3 mg/kg Q2W (N=10)<br>6 mg/kg Q4W (N=10) | <br>0.3 (0.17-0.50)<br>0.2 (0.03-1.72)<br>2.2 (0.69-6.81) | <br>50 (76.9)<br>9 (90)<br>6 (60) | No TMA, no TE | 4 patients: 2 neutralizing, 2 non-neutralizing | 16 |
| HAVEN 3 2018 | Adults and adolescents (≥12 years old) without inhibitors | 3 mg/kg QW x 4, followed by:<br>1.5 mg/kg QW (N=36)<br>3 mg/kg Q2W (N=35)<br>No prophylaxis (N=18) | <br>1.5 (0.9-2.5)<br>1.3 (0.8-2.3)<br>38.2 (22.9-63.83) | <br>18 (50)<br>14 (40)<br>0 | No TMA, no TE | None | 17 |
| HAVEN 4 2019 | Adults and adolescents with or without inhibitors | 3 mg/kg QW x 4, followed by 6 mg/kg | 4.5 (3.1-6.6) | 23 (56) | No TMA, no TE | 2 patients: 2 non-neutralizing | 18 |
| HAVEN 5 2022 | Adults and adolescents (≥12 years old) with or without inhibitors in the Asia-Pacific region | 3 mg/kg QW x 4, followed by:<br>1.5 mg/kg QW (N=29)<br>6 mg/kg Q4W (N=27)<br>No prophylaxis (N=14) | <br>1.0 (0.53-1.85)<br>1.0 (0.5-1.84)<br>27 (13.29-54.91) | <br>19 (65.5)<br>15 (55.6)<br>1 (17.1) | No TMA, no TE | 8 patients:^ 1 neutralizing, 7 non-neutralizing | 19 |
| HAVEN 6 2023 | Adults and adolescents (≥12 years old) with non-severe HA without inhibitors[$] | 3 mg/kg QW x 4, followed by: 1.5 mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg Q4W (N=73) | 0.9 (0.55-1.52) | 48 (67) | No TMA<br>1 grade 1 thrombosed hemorrhoid | 2 patients: 2 neutralizing | 20 |
| HAVEN 7[#] 2022 | Infants (≤12 months old) without inhibitors | 3 mg/kg QW x 4, followed by 3 mg/kg Q2W (N=54) | 1.9 (1.35-2.68) | 23 (42.6) | No TMA, no TE | None | 21 |

*The reduced annualized bleeding rate was preserved in the subsequent 24-week emicizumab prophylaxis period beyond the initial 24-week observation period.[80] ^Antidrug antibodies were detected in 12.5% of the predominantly Chinese participants, compared to 3.4% in HAVEN 1-4 trials with predominantly Caucasian participants. [$]Included 71% with moderate severity and 29% with mild hemophilia A. [#]Currently underway: results are from an interim analysis. Long-term assessment over a 7-year period is planned. ABR: annualized bleeding rate; 95% CI: 95% confidence interval; SAE: serious adverse events; ADA: antidrug antibodies; Ref: reference; QW: once weekly; TMA: thrombotic microangiopathy; CST: cavernous sinus thrombosis; Q2W: every 2 weeks; Q4W: every 4 weeks; TE: thromboembolic events.

**Table 2.** Interference of emicizumab with coagulation assays.

| Affected by emicizumab | Not affected by emicizumab |
|---|---|
| aPTT<br>aPTT-based single-factor assays: FVIII, FIX, FXI, FXII, protein C, protein S, APC resistance<br>Bethesda assay (clotting based) for FVIII inhibitors<br>Lupus anticoagulant | Chromogenic assays: FVIII (bovine substrate based), FIX, FXI, FXII, protein C, protein S, anti-FXa activity<br>Activated clotting time<br>Bethesda assay for FVIII inhibitors (bovine substrate based)<br>Prothrombin time<br>Thrombin time<br>Fibrinogen<br>VWF antigen and VWF:RCo activity<br>D-dimer<br>Genetic tests of coagulation factors (e.g., factor V Leiden, prothrombin 20210 mutation) |

aPTT: activated partial thromboplastin time; FVIII: factor VIII; FIX: factor IX; FXI: factor XI; FXII: factor XII; APC: activated protein C; FXa: activated factor X; VWF: von Willebrand factor; RCo: ristocetin cofactor.

accumulated from post-marketing reports and registries as of May, 2021.[33] Of these, 92% occurred in patients with pre-existing cardiovascular or thrombotic risk factors, including age over 50; 17 (45.9%) occurred in patients with inhibitors, and seven (18.9%) were associated with thrombotic occlusion of a central venous access device. Only six of the 30 individuals with non-thromboembolic events not related to a central venous access device discontinued their emicizumab prophylaxis. There were four deaths in this cohort: two patients with myocardial infarction and two elderly individuals over 70 years old with pneumonia and disseminated intravascular coagulation. Robust real-world and long-term experience with emicizumab is summarized in Table 3.[34-39] No pediatric participants have experienced thromboembolic events in the HAVEN trials and no pediatric deaths have been reported in the HAVEN series. In contrast, the real-world use of emicizumab has been associated with the death of an Israeli child, who died after developing a central venous access device-related thrombosis.[30]

Undoubtedly, with the rapid worldwide uptake of emicizumab prophylaxis regimens in HA, additional reports of thrombotic morbidity and mortality will emerge. The use of registries will be critical to monitor the safety of this and other non-factor replacement strategies. It also highlights the fact that emicizumab may not be the optimal treatment strategy for all individuals with HA with or without inhibitors and that careful selection of patients will be necessary to achieve favorable risk/benefit outcomes. The black box warnings required by the FDA in the drug's package insert serve as a reminder that the use of emicizumab may carry both known and unanticipated risks.

## Antidrug antibodies

Emicizumab was associated with the development of antidrug antibodies in 5.1% of patients (34/668) who participated in the HAVEN 1-4 clinical trials.[40] Most patients did not experience a change in emicizumab plasma concentrations or an increase in bleeding events; however, neutralizing antibodies were detected in <1% of cases and were presumed to be responsible for decreasing the plasma concentration of emicizumab and its subsequent loss of efficacy. The analysis of these antidrug antibodies indicate that there are at least two mechanisms by which they can reduce emicizumab's efficacy: by inhibiting the direct binding of emicizumab to its targets on either the FXa or FX Fab regions or by binding to the Fc region of emicizumab and thus increasing its clearance from plasma.[41,42] It should be noted that antidrug antibodies do not affect the efficacy of FVIII replacement or bypassing therapies to prevent or reverse hemorrhagic events.

The development of an anti-emicizumab antibody should be suspected when a patient experiences an increased frequency of breakthrough bleeds after having demonstrated a previously low annualized bleeding rate with emicizumab. Confirmation of neutralizing antidrug antibodies can be approached simply by demonstrating a newly prolonged aPTT and lowered one-stage FVIII or chromogenic FVIII activity with human reagents, since the aPTT should be normal and the FVIII activities high in emicizumab-treated patients. FVIII activity determined chromogenically with bovine substrate will also be very decreased.

## Breakthrough bleeding

In the pooled analysis of HAVEN 1-4 trials, there were rare breakthrough bleeds, either spontaneous or traumatic, while on emicizumab prophylaxis regimens. Over 90% of the participants had no recorded breakthrough target joint hemarthroses during up to 144 weeks of emicizumab administration. Thus, the small number of breakthrough bleeding events and improved bleeding control overall led to reduced joint morbidity; the longer the emicizumab was used, the healthier the joint became.[40] This concept was challenged by an Israeli cohort included in Table 3, in which all spontaneous bleeds occurred in previous target joints. Perhaps a hint into the mechanism of spontaneous breakthrough bleeds despite adequate hemostatic levels of emicizumab and in the absence of antidrug antibodies lies in the integrity of the fibrin clot which forms after

**Table 3. Real-world experience on emicizumab safety.**

| Cohort | N of patients | Follow-up period | SAE, N (%) | Treatment discontinuation N (%) | Breakthrough bleeds N (%) | Ref |
|---|---|---|---|---|---|---|
| Birmingham Children's Hospital | 52 | March 1, 2018 - June 15, 2021 | Total 4 (7.6)<br>Headache, 1<br>Major bleeding, 1<br>Antidrug antibody, 1<br>FVIII alloantibody inhibitor recurrence, 1<br>No TE | 3 (5.7), adverse events<br>1 (1.9), non-compliance | 12 (23) | 34 |
| Hemophilia Center of Western Pennsylvania | 42 | November 1, 2017 - May 31, 2019 | Postoperative TMA*<br>Post-surgical bleeds 4/10 | NR | 14 (33)<br>44% of these were hemarthroses | 35 |
| ATHN 7 | 152 | Through August 2021 | None | NR | NR | 36 |
| EUHASS | 985 | January 1, 2017 -December 31, 2020 | Total 4^ (0.4)<br>Myocardial infarct, 2<br>CVAD thrombosis, 1<br>SMAT, 1 | NR | NR | 37 |
| Israeli National Hemophilia Center | 70 | 18-month follow up | None⁺ | - | 36 (51) spontaneous bleeds<br>43 (61) traumatic bleeds<br>4 (5.7) significantly higher ABR# | 38,39 |

*Associated temporally with administration of activated prothrombin complex concentrate 1 month after discontinuation of emicizumab. ^One myocardial infarct and one thrombosis of a central vein access device occurred in two 78-year-old individuals who received recombinant activated factor VII, factor VIII and activated prothrombin complex concentrate along with emicizumab. One myocardial infarct and one superior mesenteric artery thrombosis occurred in younger individuals (32 years and 53 years) who received emicizumab alone. ⁺No thromboembolic events or thrombotic microangiopathy even among the five individuals over 70 years of age, or the nine individuals who had at least two cardiovascular risk factors each. #Odds of spontaneous bleeding increased by a factor of 1.029 (*P*=0.034) for every year of the patients' age. Patients with significantly higher annualized bleding rate were part of a group of elderly patients with a median age of 62.4 years, concomitantly treated with antiplatelet agents. SAE: serious adverse events; Ref: reference; FVIII: factor VIII; TE: thromboembolic events; TMA: thrombotic microangiopathy; ATHN: American Thrombosis and Hemostasis Network; EUHASS: European Haemophilia Safety Surveillance; CVAD: central venous access device; SMAT: superior mesenteric artery thrombosis; ABR: annualized bleeding rate.

thrombin is generated in plasma by emicizumab. Shimonishi *et al.* analyzed the structure of fibrin clots induced by a prothrombin/aPTT trigger reagent in the presence of emicizumab (50 μg/mL, i.e., the clinically therapeutic concentration) and showed that the fibrin structure was comparable to that of ~12% FVIII.[43] Similarly, fibrin clots generated in the presence of 100 μg/mL emicizumab had a structure equivalent to 20-30% FVIII. These *in vitro* studies indicate improved clot structure with emicizumab in HA plasma but do not provide information regarding clot stability. Fibrin clots formed in HA plasma have been demonstrated to be more fragile and weaker compared to normal control fibrin clots and appear to be more susceptible to fibrinolysis. Thus, the FVIII activity equivalence conveyed by therapeutic plasma levels of emicizumab may not accurately reflect hemostatic adequacy in all clinical scenarios.

The preferred treatments for breakthrough bleeding include infusions of rFVIIa concentrates to bypass allogeneic FVIII neutralizing antibody inhibitors and of rFVIII concentrates in the absence of FVIII inhibitors. The success of the latter strategy is based on the premise that the binding affinities of exogenously administered FVIII for both FIXa and FX are considerably higher than those of emicizumab (low-to-high nanomolar range *vs.* micromolar range), thus allowing for a competitive advantage to FVIII for FXa generation. Furthermore, FVIIIa activity in the tenase complex is modulated by circulating natural anticoagulants, i.e., activated protein C, and by spontaneous dissociation of the A2 domain, thus limiting the degree of FXa generation. This helps to prevent the development of hypercoagulability.[44]

The use of aPCC can be considered as a less optimal alternative to treat breakthrough bleeds in the presence of a FVIII inhibitor, and extreme caution is necessary to avoid creating a hypercoagulable state; dose modulation is critical (see previous discussion).

## Uncertain treatment scenarios, strategies, and benefits

### Emicizumab in males over 50 years old

The safety of emicizumab in older males with severe HA

with or without allogeneic FVIII antibody inhibitors has been a topic of concern because the drug's mechanism of action is to maintain a continuous *in vivo* procoagulant environment.

Elderly individuals with severe HA were significantly underrepresented in the HAVEN 1, 3, 4, and STASEY clinical trials. Of a total of 504 patients in the overall study population, 70 were aged 50 to 64 years and 22 were ≥65 years. There was no difference in efficacy or safety in elderly individuals compared to the younger participants in the clinical trials. The real-world experience with emicizumab therapy in individuals over 50 years of age is somewhat limited but growing rapidly. An Israeli cohort of patients older than 50 years showed the efficacy of emicizumab, with 41% of elderly individuals experiencing an annualized bleeding rate of zero, but safety concerns remain[39] (Table 3).

## Emicizumab in previously untreated patients and for immune tolerance induction strategies

The National Hemophilia Foundation of the USA and the World Federation of Haemophilia have both endorsed emicizumab as an important therapeutic option to achieve primary prophylaxis in infants with severe HA. It is recommended that primary prophylaxis is initiated at any time after birth (≤2 years old or even before the first clinical bleed), given the increased risks of developing potentially life-threatening spontaneous and traumatic intracranial hemorrhages without the initiation of primary prophylaxis. Accumulating data from the HAVEN 7 clinical trial and single institution experience have generated data to support the prophylactic efficacy and safety of emicizumab in infants. Results have shown a high percentage of zero treated bleeds and no neutralizing antidrug antibodies have been observed thus far. In addition, no deaths, no thromboembolic events, no thrombotic microangiopathy and no anti-emicizumab neutralizing antibodies have been reported.[21] One infant experienced major bleeding after circumcision while on emicizumab, and this episode was associated with suboptimal levels of thrombin generation despite administration of emicizumab.[45] Prospective and longitudinal real-world clinical safety and laboratory data in previously untreated patients are being collected.

The emergence of emicizumab as an easily administered subcutaneous procoagulant has provided a viable alternative to achieve and maintain the benefits of primary prophylaxis while mitigating many of the pitfalls of traditional FVIII replacement. Practically, primary prophylaxis using exogenous intravenous FVIII replacement at least two or three times weekly is delayed until the child is active and walking at around 12-15 months of age (ideally before the first bleed but most commonly after the first few bleeds have occurred) when traumatic bleeds are most likely to prevail, and venous access is more available. However, this approach has been associated with the development of allogeneic FVIII neutralizing inhibitory antibodies in at least 30% of previously untreated patients on primary prophylaxis.[46] FVIII inhibitors develop very rarely after the patient reaches 50 exposure days of exogenous FVIII administration. Venous access challenges, maintaining adherence to the prophylaxis protocol over time, and the financial and personal burdens of family caregivers are all additional potential potent impediments to the success of primary prophylaxis.

Primary prophylaxis based on emicizumab alone can theoretically be initiated before the first bleed and simplify the prophylaxis process in previously untreated patients. However, some treaters worry that this strategy would simply delay the emergence of FVIII inhibitors and may complicate future surgery or other bleeding scenarios in which FVIII administration will be necessary. Clinical trials are underway to compare the incidence of inhibitor development in children who receive emicizumab alone *versus* combined with concurrent FVIII replacement.

Emicizumab prophylaxis is also being studied as a component of immune tolerance induction regimens to determine the rate of inhibitor recurrence if concurrent FVIII replacement is discontinued after immune tolerance has been successfully induced. The reader is referred to a very thoughtful and comprehensive discussion of the debate on immune tolerance induction and treatment decision-making pertinent to previously untreated or minimally treated patients in the era of emicizumab.[47]

## Emicizumab for surgery

Patients who were planned to undergo surgery were excluded from the pivotal clinical trials (HAVEN 1-4), and perioperative management was at the discretion of the individual investigators. There was no specific guidance (per protocol) on surgical management provided by the sponsors and even after regulatory approval of emicizumab by the FDA and EMA, package inserts have provided no re-commendations for how to achieve, monitor, and maintain adequate hemostasis and FVIII/bypass product replacement during surgical procedures. (*https://www.hemlibra-hcp.com*) Recently, the manufacturer issued a physician/healthcare procedure (*https://www.emicizumabinfo.com*) which summarizes the most relevant published surgical experiences with emicizumab.

It is crucial to remember that emicizumab prophylaxis provides for incrementally increased hemostasis, which is equivalent to modifying a bleeding phenotype from severe to mild HA. However, emicizumab does not completely normalize hemostasis. Thus, for major surgery it is prudent in the context of a pre-existing emicizumab prophylaxis regimen to provide adjunctive procoagulant therapy with either exogenous FVIII (in the absence of an inhibitor) or with a bypassing agent (aPCC or rFVIIa) in the presence of a neutralizing allogeneic FVIII antibody inhibitor. Doses of aPCC should not exceed 50 U/kg body weight due to the potential development of thromboses

or thrombotic microangiopathy. If prolonged perioperative and postoperative treatment with aPCC is anticipated to be necessary following elective major surgery, it may be necessary to discontinue emicizumab several months prior to the operation (the elimination half-life of emicizumab is approximately 30 days). For minor surgical interventions in the context of emicizumab prophylaxis, additional procoagulant therapies may not be necessary to achieve or maintain adequate hemostasis, but patients should be closely monitored for clinical bleeding.[48] These recommendations are based on evidence from clinical trials and real-world experience, summarized in Table 4.[49-52] Standardized management as proposed by Castaman *et al.* would be ideal, but the optimal strategies remain to be determined. Most treaters agree that aPCC should be avoided in surgical scenarios to reduce thromboembolic events or thrombotic microangiopathic complications.

## Emicizumab in acquired hemophilia A

Even though acquired HA is a rare bleeding disorder (1 cases per 1-3 million population), the high mortality from hemorrhagic complications which occur in patients with this condition emphasizes the importance of effective treatments for bleeding control and for subsequent eradication of the FVIII neutralizing autoantibody by means of immunosuppression. Current treatment options to manage acquired HA include FVIII bypassing agents (rFVIIa and aPCC) and recombinant porcine (rp) FVIII.[53]

Anecdotal case reports and limited case series have described the use of emicizumab in patients with acquired HA. The usual scenario has involved administration of emicizumab to prevent recurrent bleeding events, following the initial use of rpFVIII, rFVIIa or aPCC to control the acute bleed. Dosing schemes for emicizumab for both loading and maintenance strategies have varied and the timing of the use of adjunctive immunosuppressive therapies to eradicate the inhibitor have not been standardized.[54-57]

The growing evidence of clinical benefit prompted a prospective, multicenter, single-arm, phase III clinical trial (AGEHA) in Japan to investigate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in acquired HA. Emicizumab efficacy was associated with a remarkable reduction in annualized bleeding rate from 66.4 to zero for all major bleeds. Patients received emicizumab

**Table 4.** Outcomes after surgical procedures in patients receiving emicizumab.

| Cohort | Minor procedures | Major procedures | Outcomes | Ref |
|---|---|---|---|---|
| HAVEN 1-4 trials | 215 total<br>196 (91%) without preventive treatment were neither complicated by bleeding nor required replacement therapies | 18 total*<br>15 (83%) treated pre-emptively of which 12 (80%) were neither complicated by bleeding nor required replacement therapies | No TE, TMA, ADA, recurrent anti-FVIII antibody inhibitor, deaths | 49 |
| STASEY | 56 total<br>17 (53%) without preventive treatment were neither complicated by bleeding nor required replacement therapies | 22 total^<br>18 (82%) treated pre-emptively of which 6 (33%) were neither complicated by bleeding nor required replacement therapies | No TE, TMA | 50 |
| Israeli National Hemophilia Center pediatric cohort | 16 total<br>3 (18%) without preventive treatment were neither complicated by bleeding nor required replacement therapies | - | - | 51 |
| Careggi University Hospital, Florence, Italy | 48 total<br>11 (23%) without preventive treatment were neither complicated by bleeding nor required replacement therapies | 27 total#<br>All treated pre-emptively of which 23 (85%) were neither complicated by bleeding nor required replacement therapies | - | 52 |

*Comprised five arthroplasties (27.8%), four synovectomies (22.2%) and nine others (50%), including reconstruction of femoral orthopedic hardware, open reduction of fracture, appendectomy, epidural injection, cholecystectomy, incisional hernia repair, and tonsillectomy. ^Comprised 13 arthroplasties (59%) and nine others (41%), including hemorrhoid operations, coronarography, sigmoidectomy, colostomy, laparotomy, and polypectomy. #Comprised nine arthroplasties (33%) and 18 others (67%), including lower extremity amputation, bone biopsy, arterial embolization, partial nephrectomy, transurethral prostate resection, hernia repair, ureteral catheter placement, splenectomy, cleft palate correction, muscular pseudotumor resection, and turbinate reduction. The protocol consisted of two or three boluses of 90 μg/kg recombinant activated factor VII (rFVIIa) every 3 hours at the beginning of the surgery until wound suturing, followed by 90 μg/kg rFVIIa for up to 20 days (for major orthopedic surgery) or 5-7 days (for other operations). Ref: reference; TE: thromboembolic events; TMA: thrombotic microangiopathy; ADA: antidrug antibodies; FVIII: factor VIII.

6 mg/kg subcutaneously on day 1, 3 mg/kg on day 2, and then 1.5 mg/kg once weekly from day 8 thereafter until FVIII activity exceeded 50 IU/dL without the need for exogenous coagulation factor products to treat bleeding events. All received immunosuppressive therapy. There was one asymptomatic deep vein thrombosis,[58] which was attributed to emicizumab, and which was detected 9-11 days after receiving three doses of FXIII concentrate (Fibrogammin). The patient had not received any bypassing treatments. In addition, another patient developed a non-neutralizing antidrug antibody, which did not affect plasma half-life. No onset of thrombotic microangiopathy was observed.

The optimal dosing regimen and duration of treatment with emicizumab for acquired HA remain to be elucidated. An important aspect to consider is that the long half-life of emicizumab can maintain a therapeutic effect while immunosuppression achieves low levels of inhibitor. On the other hand, once FVIII levels increase, patients might have an increased risk of thrombosis and emicizumab should be discontinued. There are two ongoing, prospective, open-label, clinical trials, being conducted in parallel in the USA (NCT05345197) and Germany (NCT04188639), which will examine the efficacy of prophylactic emicizumab administered on a scheduled basis to prevent bleeds in patients with acquired HA.

## Clinical unknowns

### Emicizumab and bone health

There is a direct relationship in severe HA (and hemophilia B) between joint and bone health. Severely decreased FVIII (<5% of normal) will predispose the joint to spontaneous and traumatic bleeds, and recurrent bleeds into the joint will cause synovial hypertrophy, cartilage deterioration, bone destruction, motion limitation and pain. Hemophilic arthropathy can be greatly impeded, if not prevented, by maintaining persistently adequate hemostasis with prophylaxis regimens with replacement of FVIII or the use of non-factor replacement strategies.

Another important consequence of severe FVIII deficiency is the development of reduced bone mineral density, which leads to abnormal bone remodeling, gait disturbance, osteopenia, and ultimately osteoporosis. This may be responsible for the increased bone fracture rate observed in individuals with severe hemophilia. Findings from FVIII-deficient mouse models suggest that decreased thrombin generation and unbalanced FVIII-von Willebrand factor complex formation may impede the osteoblastic activity needed for normal bone formation.[59,60] There is a current prospective clinical trial (NCT04131036) to examine bone and joint health over a 3-year period in patients with severe HA treated with emicizumab *versus* clotting factor prophylaxis. Biomarkers and bone density will also be assessed. Data from patients enrolled in the HAVEN 3 trial did not show significant differences in markers of bone remodeling, cartilage degradation or synthesis, questioning the need for FVIII exposure, but longer follow up may be required.[61]

With this and any other of the potential physiological roles FVIII may have,[60] the question arises as to whether individuals with severe HA who are being treated with emicizumab exclusively for its procoagulant properties will benefit incompletely from or be devoid of the long term non-hemostatic properties of FVIII. This may be most critical in the pre-adolescent years.

**Table 5.** Potential uses of emicizumab beyond hemophilia A.

| Condition | Evidence | Ref |
|---|---|---|
| Hemophilia B | Emicizumab enhanced FIX activities almost 10-fold in mild/moderate severity HB samples with wild-type FIX protein.<br>Therapeutic amounts of emicizumab corrected the deficient thrombin generation *in vitro* in samples from subjects with mild/moderate severity HB. | 63,64 |
| Factor XI deficiency | Emicizumab shortened the aPTT in severe FXI-deficient plasma samples.<br>Emicizumab modestly enhanced thrombin generation potential in FXI-deficient plasma in a dose dependent manner. | 65 |
| von Willebrand disease | Spiking type 3 VWD plasma with high emicizumab concentrations significantly increased the peak heights of thrombin generation assays.<br>Emicizumab improved thrombus formation under both high and low shear conditions in samples from patients with type 2N WVD.<br>Off-label use, case reports.<br>Pilot multicenter, prospective, open-label study of emicizumab prophylaxis in severe VWD and concomitant VWD/HA patients at least 2 years old (NCT05500807). | 66-70 |
| Reversal of therapeutic anticoagulation effects | *In vitro* studies demonstrated that emicizumab shortened the aPTT in normal non-coagulopathic plasma samples spiked with unfractionated heparin.<br>Emicizumab corrected the prolonged aPTT and attenuated thrombin generation in pooled normal plasma samples spiked with apixaban (direct anti-Xa) or argatroban (direct anti-IIa). | 24,71 |

Ref: reference; FIX: factor IX; HB: hemophilia B; aPPT: activated partial thromboplastin time; FXI: factor XI; VWD: von Willebrand disease; HA: hemophilia A; Xa: activated factor X; IIa: activated factor II.

## Additional clinical applications

The unique procoagulant properties and safety profile of emicizumab have led to the desire to determine whether this drug would be effective at reversing or preventing bleeding induced by other coagulopathies. Yada and Nogami have speculated that any bleeding disorder that has a small amount of activated factor IX available to bind to emicizumab *in vivo* might be amenable to the procoagulant benefits of increased thrombin generation by the drug[62] (Figure 2). Potential uses of emicizumab beyond HA are summarized in Table 5.[24,63-71]

## Concluding remarks

The development of extended half-life rFVIII products certainly represented a substantial progress in the treatment of HA. Nevertheless, although improvement in annualized bleeding rate has been achieved with regular injections, only a minority of patients gain absolute bleeding control or zero bleeds,[72] highlighting the need for alternative therapies. Emicizumab has revolutionized HA management. Its main advantages include subcutaneous administration and the possibility of up to monthly injections, which can improve adherence. Results from clinical trials and real-world data are encouraging, showing efficacy and achievement of zero bleeds in a substantial proportion of patients. Hence, indications for the use of emicizumab will probably be expanded to patients with moderate HA, infants with severe HA, and other coagulopathies, including von Willebrand disease and acquired HA.

However, many questions remain unanswered. The main concern, based on results from the HAVEN trials, is the risk of thromboembolic events and thrombotic microangiopathy. Yet post-marketing surveillance programs have

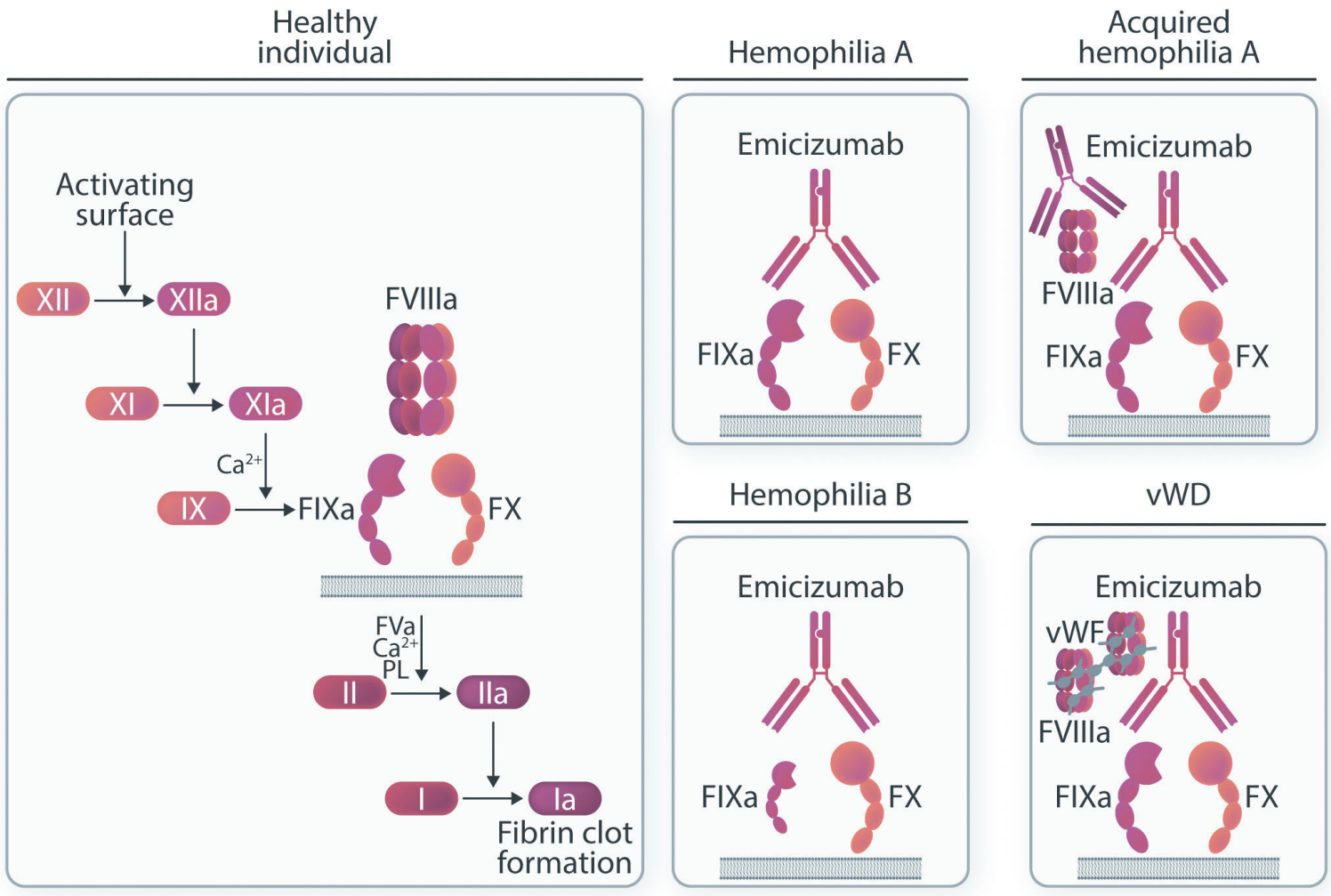


**Figure 2. Procoagulant properties of emicizumab.** Activated factor VIII (FVIIIa) is a cofactor of the intrinsic tenase complex, along with activated factor IX (FIXa) and factor X (FX). Once FX is activated, the prothrombinase complex is formed along with activated factor V (FVa) and factor II (FII aka prothrombin), which leads to thrombin generation. Emicizumab is a humanized monoclonal antibody, directed to FIXa and FX, which restores missing FVIIIa function in the tenase complex in patients with hemophilia A allowing for thrombin generation and restoring hemostasis. Emicizumab has also shown efficacy in patients with acquired hemophilia A, in whom FVIIIa function is impaired by the presence of an autoantibody. *In vitro* studies have shown that even small amounts of FIXa are enough to guarantee effective hemostasis, making emicizumab a potential treatment option for patients with mild and moderate hemophilia B. In patients with von Willebrand disease, particularly type 3, levels of both von Willebrand factor and FVIII are markedly reduced because von Willebrand factor prevents degradation and clearance of FVIII. It is therefore reasonable that emicizumab, in the presence of FIXa, could restore hemostasis in patients with von Willebrand disease. Before the intrinsic tenase complex is formed, FIX is activated by FXIa. *In vitro* studies have shown that emicizumab restores thrombin generation in FXI-deficient plasma, but it is unclear if this is due to residual FIXa levels, which are required for the procoagulant effect of emicizumab. PL: phospholipids; vWD: von Willebrand disease; vWF: von Willebrand factor.

shown that risk mitigation strategies, including judicious use of other therapies, such as aPCC, are effective.[33] Another area of uncertainty is the management of breakthrough bleeding, which a minority of patients experience. Similarly, more data are needed regarding the management of patients undergoing surgical procedures, and regarding the risks of thrombosis and bleeding in elderly individuals using emicizumab concomitantly with antiplatelet and/or anticoagulant agents.

The pursuit of the ideal treatment for HA continues. The success of emicizumab has led to the development of a new generation of FVIII-mimetic bispecific antibodies, NXT007 and Mim8, which are currently in phase I/II studies.[73,74] Betting on the benefits of using FVIII, a new extended half-life rFVIII molecule was created by fusing a dimeric Fc fragment and two XTEN polypeptides to B-domain-deleted rFVIII to achieve a longer circulating half-life. In addition, the D'D3 domain of von Willebrand factor (the physiological FVIII binding site), was appended to the fusion FVIII-Fc molecule in order to circumvent the limitations to prolonging plasma half-life extension imposed by FVIII- von Willebrand factor complex formation, as occurs with all previously available commercial FVIII replacement products.[75] Efanesoctocog alfa (BIVV001) has been shown to achieve adequate FVIII plasma activity levels with weekly infusions, resulting in a 77% reduction in the mean annualized bleeding rate, resolution of bleeding episodes in most patients, and improvement in pain and quality of life.[76] A long-term safety and efficacy evaluation is planned (NCT04644575). Advantages of efanesoctocog alfa include its use to treat breakthrough bleeding episodes and in the perioperative setting with a simplified weekly regimen.

To rebalance hemostasis, new treatment options are being explored. Fitusiran, a small interfering RNA that decreases hepatic synthesis of antithrombin, has shown a significant decrease in annualized bleeding rate with the advantage of monthly subcutaneous administration, making it a promising product.[77] Concizumab, a monoclonal anti-tissue factor pathway inhibitor (TFPI) antibody has also shown comparable results, as far as concerns annualized bleeding rate, with once-daily subcutaneous administration.[78] However, thromboembolic events seen in the early phases of development of these products remain a source of concern and longer follow-up is needed. Marstacimab is another anti-TFPI monoclonal antibody with the advantage of weekly subcutaneous dosing. It has shown promising results after 1 year of follow-up and is currently in a phase III study.[79] A summary of available treatments is shown in Table 6.

Finally, efforts to find a cure for patients with HA continue. Although gene therapy is beyond the scope of this review, it

**Table 6.** Available treatment options for patients with hemophilia A, including extended half-life recombinant factor VIII products and non-factor related products.

| Product | Manufacturer | Structure/ mechanism of action | Route of administration | Frequency of administration | Plasma half-life |
|---|---|---|---|---|---|
| **Recombinant FVIII products** | | | | | |
| Efmoroctocog alfa (Elocta/Eloctate) | Sobi | Fc-fusion | IV | 3-5 days interval | 19 hours |
| Rurioctocog alfa pegol (Adynovi/Adynovate) | Baxalta/Takeda | PEGylated | IV | 2 times per week | 14-16 hours |
| Damoctocog alfa pegol (Jivi) | Bayer | PEGylated | IV | 2 times per week | 19 hours |
| Turoctocog alfa pegol (Esperoct) | Novo Nordisk | GlycoPEGylated | IV | 3-5 days interval | 18-19 hours |
| Efanesoctocog alfa (Altuviiio) | Sobi/Sanofi | Fusion to Fc, 2 XTEN polypeptides and D'D3 VWF domain | IV | Weekly | 43 hours |
| **Non-factor products** | | | | | |
| Emicizumab (Hemlibra) | Genentech, Roche | Bi-specific FVIII-mimetic monoclonal antibody | SC | Every 1, 2 or 4 weeks | 30 days |
| Concizumab (Alhemo) | Novo Nordisk | Anti-TFPI monoclonal antibody | SC | Daily | 38 hours |
| Fitusiran | Sanofi | siRNA targeting antithrombin | SC | Monthly | 3-5 hours |
| Marstacimab | Pfizer | Anti-TFPI monoclonal antibody | SC | Weekly | 33-65 hours |

FVIII: factor VIII; IV: intravenous; VWF: von Willebrand factor; SC: subcutaneous; TFPI: tissue factor pathway inhibitor; siRNA: small interfering RNA.

might be a feasible option in the future. Limitations include variable durability of effectiveness, inability to predict the extent of FVIII incremental response, hepatotoxicity, development of antibodies against the vector, availability in children, and the cost of gene therapy acquisition.

With multiple treatment options available, it is an exciting time for the hemophilia field. Patients and providers will face challenging decisions when choosing the optimal therapy, especially considering that head-to-head comparisons between emicizumab and other treatments are unlikely to be done. Emicizumab has certainly been a game-changer, with robust data showing its safety and efficacy, but the game has not ended. If gene therapy is also approved in children, this will probably be the ideal option for children and young adults who are more likely to look for a cure. Extended half-life FVIII products with improved pharmacokinetics that guarantee better adherence to treatment will continue to be critical in the management of patients with cardiovascular and thromboembolic risk factors, as well as patients with breakthrough bleeds and in the perioperative setting. Replacement products, which reset hemostatic balance by interfering with the inhibitory and modulatory mechanisms of normal coagulation pathways, e.g., antithrombin and TFPI, are bringing further innovation to the field. HA therapies have joined the era of precision medicine.

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**Contributions**

*PEAA, PMM and CMK contributed equally to writing and editing this manuscript.*

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