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by Pedro E. Alcedo Andrade, Pier Mannuccio Mannucci, and Craig M. Kessler

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Emicizumab: the hemophilia A game changer

Pedro E Alcedo Andrade¹, Pier Mannuccio Manucci², Craig M Kessler¹

¹ Georgetown University Medical Center, Lombardi Comprehensive Cancer Center, Washington, District of Columbia, USA.

² Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Angelo Bianchi Bonomi, Hemophilia and Thrombosis Center, Milan, Italy.

Corresponding author: Craig M Kessler, kesslerc@gunet.georgetown.edu

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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 article describes the research steps behind the development of this game-changer medication, its success for the prophylaxis of bleeding episodes as witnessed by the results of pivotal clinical trial but also by real life use in the frame of a still expanding global market. We shall also discuss potential and actual adverse events and the nuances related to clinical use such as laboratory monitoring, development of neutralizing anti-drug-antibodies, risk of thrombosis/hypercoagulability and use in the management of surgical operations. The potential of using emicizumab to prevent bleeding in other congenital and acquired coagulation disorders will also be sketched.

Introduction

The history of hemophilia A (HA) treatment has been marked with solid innovation and progress, intended to improve the quality of life of individuals with this bleeding disorder. Emicizumab has contributed in a major way in 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 inhibitor patients and by Manco-Johnson et al. for inhibitor free patients (2, 3). Both studies demonstrated that prophylaxis with infusions of anti-inhibitor complex by-pass activity concentrates or of recombinant factor VIII (rFVIII), versus on-demand therapy prevent joint damage and decrease the frequency of joint and other hemorrhages in individuals with severe HA with and without inhibitors. The main impediments to success of such regimens have been adherence to the demands of predominant twice weekly intravenous protocols for factor administration and the availability over time of functional venous access infusion sites. With the development and introduction of the recombinant, humanized, bispecific FVIII-mimetic procoagulant antibody, emicizumab, into the therapeutic armamentarium, the subcutaneous (SQ) administration of hemostatic agents has improved adherence with equivalent safety and efficacy profiles compared to recombinant and plasma-derived concentrates for HA with and without inhibitors.

This review will describe the history and pharmacology behind the development of emicizumab; its 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 will also discuss complications and the nuances associated with its use, such as laboratory monitoring; development of specific neutralizing anti-drug antibodies; thrombotic/hypercoagulability potential; and it will show why this game changer medication continues to capture an ever-expanding global market share among the hemostatic agents commercially available for the prevention of hemorrhagic episodes in 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”. Kitazawa and Shima ascribed to Dr. Kunihiro Hattori the concept of binding FIXa to FX via a bispecific antibody to function as the FVIII cofactor (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 PK modeling and model-based simulations derived from phase 1/2 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 3 HAVEN trials: a SQ loading dose of 3 mg/kg once weekly for a total of 4 weeks and three different SQ maintenance doses starting at week 5 that included 1.5 mg/kg once every week, 3 mg/kg once every two weeks or 6 mg/kg once every four weeks. All regimens have shown comparable efficacy and similar side effect profiles.

Pivotal Clinical Trials: Establishing Efficacy and Safety

In the era of very effective FVIII replacement therapies resulting in median annualized bleeding rate (ABR) close to 0 in most individuals with severe HA, the development of neutralizing anti-FVIII inhibitors has emerged as the highest priority complication of repeat exposures to administered 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 activated prothrombin complex concentrates (aPCC) and recombinant activated factor VII (rFVIIa). In practice, these products provided adequate hemostatic efficacy, which was however 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 SQ non-factor FVIIIa mimetic with durable effectiveness was greatly anticipated when the HAVEN 1 (15) and 2 (16) clinical trials were launched. These phase 3 studies assessed the efficacy, safety, and pharmacokinetics of once-weekly SQ 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 broad the scope of emicizumab use, including patients without inhibitors (HAVEN 3 and 4) (17, 18), patients of the Asia-Pacific region (HAVEN 5) (19), non-severe HA (HAVEN 6) (20) and infants (HAVEN 7) (21). Different dosing regimens were evaluated showing 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 34th best-selling pharmaceutical of 2022 (23). Its availability in developing nations is also well-established following distribution of 2,528,730 milligrams by the World Federation of Haemophilia to 806 patients in Africa, Latin America, Asia, and Eastern Europe. 55% of these individuals were under 12 years old and 64% were non-inhibitor patients (22).

Practical Therapeutic Concerns and Questions

Laboratory Testing

As the use of emicizumab increases, there has been 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 immunologic or chromogenic techniques are not affected (24, 25); see Table 2.

Global coagulation testing techniques have been proposed to estimate the hemostatic potential of emicizumab. Thrombin generation assays (TGA) and thromboelastography (TEG) 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, TGA 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, the TGA may lead to overconfidence and faulty clinical decision making regarding the hemostatic response to emicizumab. It has been suggested that TGA may best be used to limit the occurrence of adverse thromboembolic events (TE) 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, when five patients experienced TE when emicizumab was combined with multiple high doses of aPCC. In vitro plasma spiking studies corroborated the marked synergistic effects on TGA when aPCC was added to emicizumab (29). However, despite suggestions that there is 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 their unique modes of action to activate FX and to the vagaries in the biochemical assays methods (28). Kitazawa et al. approached this issue by developing a primate bleed model of AHA (31). Using rFVIII as the FVIII calibrator, the therapeutic emicizumab level of about 55 microgram/mL had an estimated FVIII equivalence activity level

of 10%-20% (28). The HAVEN 1 study demonstrated a steady state mean emicizumab level to be 55 microgram/mL (range 35-70). Even though emicizumab assays are becoming more available commercially, it is anticipated that their use will be somewhat limited, perhaps to confirm patient 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. have summarized the adverse events recorded in all the HAVEN clinical trials (32). The most frequently observed adverse event was 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%. Anaphylaxis is extremely rare. There were 2 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 TE and thrombotic microangiopathy (TMA), as summarized in Table 1. Critically, these complications were associated with concomitant replacement therapy with aPCC at accumulative doses over 100 U/kg/day/24 hours for more than one day. An updated summary of TE reported 37 additional cases of non-aPCC related events accumulated from post marketing reports and registries as of May, 2021 (33). Of these, 92% had preexisting cardiovascular or thrombotic risk factors, including age over 50; 17 (45.9%) occurred in patients with inhibitors, and 7 (18.9%) were associated with thrombotic occlusion of their central venous access devices (CVAD). Only 6 of the 30 individuals with non-CVAD-related TE discontinued their emicizumab prophylaxis. There were 4 deaths in this cohort: 2 with myocardial infarctions; one gastrointestinal bleed; and 2 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 TE 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 after developing a CVAD-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 and without inhibitors and that careful patient selection will be necessary to achieve favorable risk/benefit outcomes. The black box warnings required by the FDA in its package insert serves as a reminder that use of emicizumab may carry known and unanticipated risks.

Anti-Drug Antibodies

Emicizumab was associated with the development anti-drug-antibody (ADA) 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 ADA indicates that there are at least 2 mechanisms by which they can reduce emicizumab 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 ADA do not affect the efficacy of FVIII replacement or by-pass therapies to prevent or reverse hemorrhagic events.

The development of an anti-emicizumab antibody should be suspected when a patient experiences increased frequency of breakthrough bleeds after having demonstrated a previously low ABR with emicizumab. Confirmation of neutralizing ADAs can be approached simply by demonstrating a newly prolonged aPTT and lowered one stage FVIII or chromogenic FVIII

activity with human reagents, since in emicizumab treated patients the aPTT should be normal and the FVIII activities high. Chromogenic FVIII activity with bovine substrate will also be very decreased.

Breakthrough Bleeding Events

In the pooled analysis of HAVEN 1-4, there were rare breakthrough bleeds, either spontaneous or traumatic, while on emicizumab prophylaxis regimens. Over 90% had no recorded breakthrough target joint hemarthroses up to 144 weeks of emicizumab. Thus, the small number of breakthrough bleeding events and improved bleed control overall led to reduced joint morbidity; the longer the emicizumab was used, the healthier the joint became (40). This hypothesis was challenged by an Israeli cohort included in Table 3, where all spontaneous bleed occurred in previous target joints.

Perhaps a hint into the mechanism for spontaneous breakthrough bleeds despite adequate hemostatic levels of emicizumab and in the absence of ADA lies in the integrity of the fibrin clot which forms after thrombin is generated in plasma by emicizumab. Shimonishi et al. analyzed the structure of fibrin clots induced by a PT/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 possessed 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. The stability of fibrin clots formed in HA plasma have been demonstrated to be more fragile and weaker compared to normal control fibrin clots and these clots appear to be more susceptible to fibrinolysis. Thus, the factor VIII 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 events include infusions of rFVIIa concentrates for by-passing allo-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 allo-FVIII antibody inhibitors has been a topic of concern because its 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 versus 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 efficacy of emicizumab, with 41% of elderly individuals experiencing a zero annualized bleeding but safety concerns remain (39); see 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 to be an important therapeutic option to achieve primary prophylaxis in infants with severe HA. It is recommended to initiate primary prophylaxis 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 ADA have been observed thus far. In addition, no deaths, no TE, no TMA nor anti-emicizumab neutralizing antibodies have been reported (21). One infant experienced major bleeding post 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 PUPS is being collected.

The emergence of emicizumab as an easily administered SQ 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 2-3 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 allo-FVIII neutralizing inhibitory antibodies in at least 30% of PUPS 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 familial caregivers are all additional potential potent impediments to the success of primary prophylaxis.

Emicizumab only-based primary prophylaxis can theoretically be initiated before the first bleed and simplify the prophylaxis process in PUPS. However, some treaters worry that this strategy would simply delay the emergence of FVIII inhibitors and may complicate future surgeries or

other bleeding scenarios when FVIII administration will be necessary. Clinical trials are under way 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 (ITI) regimens to determine the rate of inhibitor recurrence if concurrent FVIII replacement is discontinued after successful ITI. The reader is referred to a very thoughtful and comprehensive discussion of the debate on ITI and treatment decision making pertinent to PUPs/MTPs in the era of emicizumab (47).

Emicizumab for Surgeries

Patients with planned surgeries 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 recommendations 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 [emicizumabinfo.com] which summarizes the most relevant published surgical experiences with emicizumab.

It is critical 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 bypass therapy (aPCC or rFVIIa) in the presence of a neutralizing allo-FVIII antibody inhibitor. Doses of aPCC should not exceed 50 U/kg body weight due to the potential development of thromboses or TMA. If prolonged peri and post operative treatment with aPCC is anticipated to be necessary following an elective major surgery, it may be necessary to discontinue emicizumab several months prior to surgery (elimination half-life of emicizumab is approximately 30 days). For minor surgeries 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 TE or TMA complications.

Emicizumab in Acquired Hemophilia A (AHA)

Even though AHA is a rare bleeding disorder (1 case per 1-3 million population), the high mortality from hemorrhagic complications which occur in this patient population stresses the importance of effective treatments for bleeding control and for subsequent eradication of the autoantibody FVIII neutralizing antibody by means of immunosuppression. Current treatment options to manage AHA 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 AHA. The usual scenario has involved administration of emicizumab to prevent recurrent bleeding events, following the initial use of rpFVIII, recombinant activated FVII 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 3 clinical trial (AGEHA) in Japan, to investigate the safety, efficacy, pharmacokinetics, and pharmacodynamics of emicizumab in AHA. Emicizumab efficacy was associated with a remarkable reduction in ABR from 66.4 to 0 for all major bleeds. Patients received emicizumab 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 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 3 doses of FXIII concentrate (Fibrogammin). The patient had

not received any by-pass therapies. In addition, another patient developed a non-neutralizing ADA, which did not affect plasma half-life. No onset of TMA was observed.

The optimal dosing regimen and duration of treatment with emicizumab for AHA 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 increased risk of thrombosis and emicizumab should be discontinued. There are two ongoing perspective open label clinical trials, being conducted in parallel in the United States (NCT05345197) and Germany (NCT04188639), which will examine the efficacy of prophylactic emicizumab administered on a scheduled basis to prevent bleeds in patients with AHA.

Clinical Unknowns

Emicizumab and Bone Health

There is a direct relationship in severe HA (and hemophilia B (HB)) 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 (VWF) complex formation may impede osteoblast 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 vs clotting factor prophylaxis.

Biomarkers and bone density will also be assessed. Data from patients enrolled in HAVEN 3 trial did not show significant difference in markers of bone remodeling, cartilage degradation and synthesis, questioning the need for FVIII exposure, but longer follow up may be required (61).

With this and any other of the potential physiologic 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 incompletely benefit from or be devoid of the long term non-hemostatic properties of FVIII. This may be most critical in the pre-adolescent years.

Additional Clinical Applications

The unique procoagulant properties and safety profile of emicizumab have led to the desire to determine if this drug would have efficacy to reverse or prevent bleeding induced by other coagulopathies. Yada and Nogami have speculated that any bleeding disorder which has a small amount of FIXa available to bind to emicizumab in vivo might be amenable to the procoagulant benefits of increased thrombin generation by emicizumab (62). Potential uses of emicizumab beyond HA are summarized on Table 5 (24, 63-71).

CONCLUSIVE REMARKS

The development of EHL rFVIII products certainly represented a substantial progress in the treatment of HA. Although improvement in ABR 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. Main advantages include SQ 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 will probably be expanding to

patients with moderate HA, infants with severe HA, and other coagulopathies, including von Willebrand disease and acquired hemophilia A.

However, many questions remain unanswered. The main concern is the risk of TE and TMA based on results from the HAVEN trials. Yet post marketing surveillance programs have shown that risk mitigation strategies, including judicious use of other therapies like aPCC, are effective (33). Another area of uncertainty is the management of breakthrough bleeding that a minority of patients experience. Similarly, more data are needed regarding the management of patients undergoing surgical procedures, and regarding the thrombosis and bleeding risks of using emicizumab in elderly individuals with concomitant use of antiplatelet and/or anticoagulant agents.

The pursuit for the ideal treatment for HA continues. The success of emicizumab has led to development of a new generation of FVIII mimetic bispecific antibodies, NXT007 and Mim8, which are currently on phase I/II studies (73, 74). Betting on the benefits of using FVIII, a new EHL rFVIII molecule was created by fusing a dimeric Fc fragment and two XTEN polypeptides to B-domain deleted rFVIII to achieve circulating half-life extension. In addition, the D'D3 domain of VWF (the physiological FVIII binding site), was appended to the fusion FVIII-Fc molecule in order to circumvent the limitations to prolong plasma half-life extension imposed by FVIII-VWF 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 ABR, resolution of bleeding episodes in most of the 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 interference RNA that decreases hepatic synthesis of antithrombin, has shown a significant decrease in ABR with the advantage of monthly SQ administration, making it a promising product (77). Concizumab, a monoclonal anti-TFPI antibody has also shown comparable results as far as ABR with a once-daily SQ administration (78). However, TE seen in the early phases of development of these products remains a source of concern and longer follow-up is needed.

Marstacimab is another anti-TFPI monoclonal antibody with the advantage of weekly SQ dosing, which has shown promising results after one year follow up and is currently on phase 3 (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 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 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. EHL FVIII with improved pharmacokinetics that guarantee improved adherence will continue to be critical in the management of patients with cardiovascular risk factors and TE, 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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Table 1. Summary of results from HAVEN clinical trials

Study	Population	Doses	ABR (median)	Zero bleed rates, N (%)	SAE, N	ADA	Reference
HAVEN 1 2017	Adults and adolescents (≥ 12 years old) with inhibitors	3.0 mg/kg QW x 4, followed by 1.5 mg/kg QW (n = 35) No prophylaxis (n = 18)	2.9* (95% CI, 1.7 to 5.0) 23.3 (95% CI, 12.3 to 43.9)	22 (63%) 1 (6%)	2 TMA 1 CST 1 Superficial thrombophlebitis	None	(15)
HAVEN 2 2019	Children (< 12 years old) with inhibitors	3.0 mg/kg QW x 4, followed by: 1.5 mg/kg QW (n = 68) 3.0 mg/kg Q2W (n = 10) 6 mg/kg Q4W (n = 10)	0.3 (95% CI, 0.17 to 0.50) 0.2 (95% CI, 0.03 to 1.72) 2.2 (95% CI, 0.69 to 6.81)	50 (76.9%) 9 (90%) 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	3.0 mg/kg QW x 4, followed by: 1.5 mg/kg QW (n = 36) 3.0 mg/kg Q2W (n = 35) No prophylaxis (n = 18)	1.5 (95% CI, 0.9 to 2.5) 1.3 (95% CI, 0.8 to 2.3) 38.2 (95% CI, 22.9 to 63.83)	18 (50%) 14 (40%) 0	No TMA, no TE	None	(17)
HAVEN 4 2019	Adults and adolescents (≥ 12 years old) with or without inhibitors	3.0 mg/kg QW x 4, followed by 6 mg/kg Q4W (n = 41)	4.5 (95% CI, 3.1 to 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	3.0 mg/kg QW x 4, followed by:			No TMA, no TE	8 patients^: 1 neutralizing, 7 non-	(19)

	inhibitors in the Asia-Pacific region	1.5 mg/kg QW (n = 29)	1.0 (95% CI, 0.53 to 1.85)	19 (65.5%)		neutralizing	
		6.0 mg/kg Q4W (n = 27)	1.0 (95% CI, 0.5 to 1.84)	15 (55.6%)			
		No prophylaxis (n = 14)	27 (95% CI, 13.29 to 54.91)	1 (17.1%)			
HAVEN 6 2023	Adults and adolescents (≥ 12 years old) with non-severe HA without inhibitors	3.0 mg/kg QW x 4, followed by: 1.5 mg/kg QW, 3.0 mg/kg Q2W, or 6 mg/kg Q4W (n = 73)	0.9 (95% CI, 0.55 to 1.52)	48 (67%)	No TMA 1 grade 1 thrombosed hemorrhoid	2 patients: 2 neutralizing	(20)
HAVEN 7# 2022	Infants (≤ 12 months old) without inhibitors	3.0 mg/kg QW x 4, followed by 3.0 mg/kg Q2W (n = 54)	1.9 (95% CI, 1.35 to 2.68)	23 (42.6%)	No TMA, no TE	None	(21)

* Durability of reduced ABR was preserved in the subsequent 24-week emicizumab prophylaxis period beyond the initial 24-week observation period (80).

^ ADAs were detected in 12.5% of the predominant Chinese participants, compared to 3.4% ADA incidence in HAVEN 1-4 trials with predominant Caucasian participants

\$ Included 71% moderate severity, 29% mild

Currently underway. Results are from interim analysis. Long term assessment over a 7-year period is planned

ABR: annualized bleeding rate; ADA: anti-drug antibodies; CST: cavernous sinus thrombosis; QW: once weekly; Q2W: every 2 weeks; Q4W: every 4 weeks; SAE: serious adverse events; TE: thromboembolic events; TMA: thrombotic microangiopathy

Table 2. Interference of emicizumab with coagulation assays

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

APC: activated protein C; VWF: von Willebrand factor

Table 3. Real-world experience on emicizumab safety.

Cohort	Number of patients	Follow up period	SAE, n (%)	Treatment discontinuation, n (%)	Breakthrough bleeds, n (%)	Reference
Birmingham Children's Hospital	52	March 1, 2018 – June 15, 2021	Total 4 (7.6%) Headache, 1 Major bleeding, 1 ADA, 1 FVIII alloantibody inhibitor recurrence, 1 No TE	3 (5.7%), adverse events 1 (1.9%), non-compliance	12 (23%)	(34)
Hemophilia Center of Western Pennsylvania	42	November 1, 2-17 – May 31, 2019	Postoperative TMA* Post-surgical bleeds 4/10	None reported	14 (33%) 44% of these were hemarthrosis	(35)
ATHN 7	152	Through August 2021	None	None reported	None reported	(36)
EUHASS	985	January 1, 2017 – December 31, 2020	Total 4 [^] (0.4%) MI, 2 CVAD thrombosis, 1 SMAT, 1	None reported	None reported	(37)
Israeli National Hemophilia Center	70	18 month follow up	None+		36 (51%) spontaneous bleeds 43 (61%) traumatic bleeds 4 (5.7%) significantly higher ABR#	(38, 39)

ATHN: American Thrombosis and Hemostasis Network; CVAD: central venous access device; EUHASS: European Haemophilia Safety Surveillance; MI: myocardial infarction; SAE: serious adverse events; SMAT: superior mesenteric artery thrombosis; TE: thromboembolic events; TMA: thrombotic microangiopathy

*Associated temporally with aPCC administration one month after discontinuation of emicizumab

[^]One MI and one CVAD thrombosis occurred in two 78 years old individuals who received rFVIIa, FVIII and aPCC along with emicizumab. One episode of MI and one SMAT occurred in younger individuals (32 years and 53 years) that received emicizumab alone.

+No TE or TMA even within the 5 individuals over 70 years of age, or the 9 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 patient age. Patients with significantly higher ABR were part of a group of elderly patients with median age of 62.4 years, concomitantly treated with antiplatelet agents.

Table 4. Outcomes after surgical procedures in patients receiving emicizumab

	Minor procedures	Major procedures	Outcomes	Reference
HAVEN 1 – 4 trials	215 total 196 (91%) without preventing treatment were not complicated by bleeding nor required replacement therapies	18 total* 15 (83%) treated preemptively of which 12 (80%) were not complicated by bleeding nor required replacement therapies	No TE, TMA, ADA, recurrent anti-FVIII antibody inhibitor, deaths	(49)
STASEY	56 total 17 (53%) without preventing treatment were not complicated by bleeding nor required replacement therapies	22 total^ 18 (82%) treated preemptively of which 6 (33%) were not complicated by bleeding nor required replacement therapies	No TE, TMA	(50)
Israeli National Hemophilia Center pediatric cohort	16 total 3 (18%) without preventing treatment were not complicated by bleeding nor required replacement therapies			(51)
Careggi University Hospital, Florence, Italy	48 total 11 (23%) without preventing treatment were not complicated by bleeding nor required replacement therapies	27 total# All treated preemptively of which 23 (85%) were not complicated by bleeding nor required replacement therapies		(52)

*Included 5 arthroplasties (27.8%), 4 synovectomies (22.2%) and 9 others (50%), including reconstruction of femoral orthopedic hardware, open reduction of fracture, appendectomy, epidural injection, cholecystectomy, incisional hernia repair, and tonsillectomy

^Included 13 arthroplasties (59%) and 9 others (41%) including hemorrhoid operations, coronarography, sigmoidectomy, colostomy, laparotomy, and polypectomy

#Included 9 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. Protocol consisted of 2 – 3 bolus of 90 µg/kg rFVIIa every 3 hours at the beginning of the surgery until wound suturing, followed by 90 µg/kg rFVIIa at for up to 20 days (in major orthopedic surgeries) or 5 – 7 days (in other surgeries),

Table 5. Potential uses of emicizumab beyond hemophilia A

Condition	Evidence	Reference
Hemophilia B	Emicizumab enhanced almost tenfold FIX activities in mild/moderate severity HB samples with wild-type FIX protein. Therapeutic amounts of emicizumab corrected the deficient thrombin generation in vitro in samples from mild/moderate severity HB.	(63, 64)
Factor XI deficiency	Emicizumab shortened the aPTT in severe FXI-deficient plasma samples. 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 increased significantly the peak heights of thrombin generation assays. Emicizumab improved thrombus formation under both high and low shear conditions in samples from patients with type 2N WVD Off label use, case reports 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 have demonstrated that emicizumab shortened the aPTT in normal non-coagulopathic plasma samples spiked with unfractionated heparin. Emicizumab corrected the prolonged aPTT and attenuated thrombin generation in pooled normal plasmas spiked with apixaban (direct anti-Xa) or argatroban (direct anti-IIa).	(24, 71)

HB: Hemophilia B; VWD: von Willebrand disease

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

IV: intravenous; rFVIII: recombinant factor VIII; siRNA: small interfering RNA; SQ: subcutaneous; TFPI: tissue factor pathway inhibitor; VWF: von Willebrand factor

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 FVIIIa-cofactor activity, leading to the development of ACE910, subsequently named Emicizumab. In vivo studies were developed using AHA primate models, where bleeding events were successfully treated and prevented, and a once-weekly SQ dosing provided the rationale for a prophylaxis protocol in HA patients.

The first in-human study started in 2013, designed as a randomized, placebo-controlled, phase 1 trial using a single SQ Emicizumab dose in healthy volunteers, which demonstrated efficacy, high bioavailability from SQ administration, without evidence of hypercoagulability. These findings were corroborated in short-term and long-term extension studies (12 week to 33.3 months, respectively) of weekly SQ administration to severe HA patients over 12 years old with and without inhibitors, which also showed a decrease in ABR close to zero, regardless of the presence of inhibitors, and four cases of ADA, which were non-neutralizing and did not cause changes in treatment.

ABR: annualized bleeding rate; ADA: anti-drug antibodies; AHA: acquired hemophilia A; HA: hemophilia A; SQ: subcutaneous; TE: thrombotic events.

Figure 2. Procoagulant properties of Emicizumab

FVIIIa is a cofactor of the intrinsic tenase complex, along with FIXa and FX. Once FX is activated, the prothrombinase complex is formed along with FVa and FII, 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 HA allowing for thrombin generation and restoring hemostasis. In patients with AHA, where FVIIIa function is impaired by the presence of an autoantibody, Emicizumab has also shown efficacy.

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 HB.

In patients with vWD, particularly type 3, both levels of vWF and FVIII are markedly reduced because vWF prevents degradation and clearance of FVIII. It is therefore reasonable that Emicizumab, in the presence of FIXa, could restore hemostasis in patients with WVD.

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 Emicizumab procoagulant effect.

AHA: acquired hemophilia A; HA: hemophilia A; HB: hemophilia B; PL: phospholipids; vWD: von Willebrand disease; vWF: von Willebrand factor

01.

2000

Research & development



- ACE910
- Synthesized using Chinese hamster ovary cell system
- 145.6 kDa, similar to IgG (150 kDa)

02.

Preclinical studies



- *In vivo* studies
- Feasible subcutaneous administration
- 100% bioavailability
- Half-life 30 days
- No thrombotic events
- No thrombotic events
- One anti-drug antibodies

03.

2013

Human studies

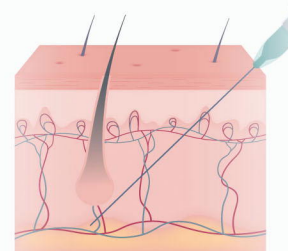


- Phase I
- Promising efficacy based on annualized bleeding rate
- No thrombotic events
- Four anti-drug antibodies

04.

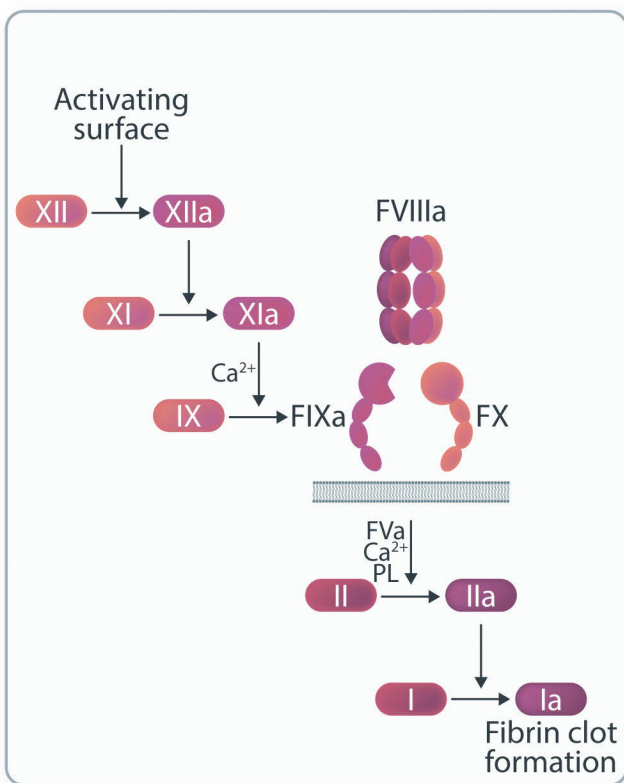
2017

Clinical trials

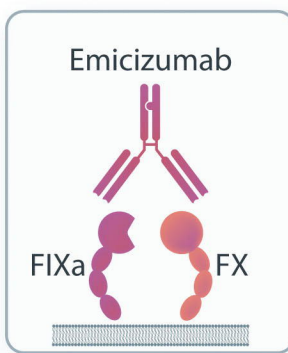


- Pivotal phase 3 HAVEN clinical trials

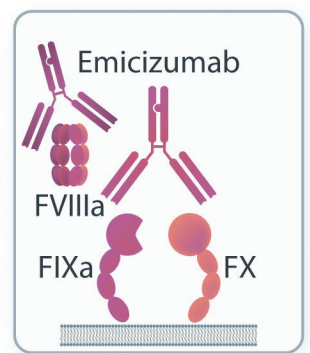
Healthy individual



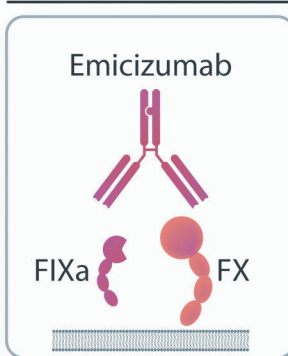
Hemophilia A



Acquired hemophilia A



Hemophilia B



vWD

