REVIEW ARTICLE

Emicizumab revolution in treating Hemophilia

Alaa Mukhtar[1], Gehan L Abdel Hakeem[1], Rawhya Elshereef[2], Eman El-Tahlawy[3], Mohamed A Bahaa El-deen[1]

[1]*Department of Pediatrics, Faculty of Medicine, Minia University,Egypt*
[2]*Department of Rheumatology and Rehabilitation, Faculty of Medicine, Minia University,Egypt*
[3]*Medicine Department, Division of Environmental Research, National Research Centre, Giza, Egypt*

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ABSTRACT

HemophiliaA (H.A.) has beenanuncommon hereditary X-linked bleeding disorder indicated by clotting factorVIII (FVIII) deficiency, leading to impaired hemostasis. H.A. affects approximately one in 5,000male births in the U.S., often resulting in spontaneous joint bleeding, chronic pain, and an increased risk of cerebral hemorrhage. Prophylactic treatment with FVIII replacement or the bispecific antibody emicizumab has become a crucial strategy to prevent bleeding episodes and long-term tissue damage. Emicizumab, approved by the FDA & EMA in2018, mimics FVIII activity by binding to activated factorIX (FIXa) &factorX (F.X.), facilitating blood clotting regardless of FVIII inhibitors.

The development of emicizumab involved extensive bioengineering to optimize its safety, stability, and efficacy, leading to its successful application in clinical trials. These trials demonstrated that emicizumab significantly decreases the annualized bleeding rate in studied cases with or without inhibitors, including severe H.A. cases, with a favorable safety profile and minimal adverse events. Emicizumab's subcutaneous administration, high bioavailability, and predictable pharmacokinetics make it a practical option for H.A. prophylaxis.

Despite its benefits, emicizumab can interfere with specific coagulation assays and may develop anti-drug antibodies (ADAs) in rare cases, potentially reducing its efficacy. Ongoing research and post-marketing surveillance continue to assess its long-term safety and effectiveness, making emicizumab a transformative treatment in managing hemophilia A.

Keywords: Emicizumab, Hemophilia.

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INTRODUCTION

Haemophilia is a debilitating chronic illness that significantly affects patients' quality of life. During continuous research for the best treatment options, the easily subcutaneously administered bispecific emicizumab antibody was approved for prophylactic therapy for both inhibited and non-inhibited hemophilia victims.

The novel non-factor therapy solved the problem of patients' adherence, markedly decreased the annual bleeding rates, marvelously improved their quality of life, and considerably lessened the disabling complications, including arthropathy. With emicizumab's low incidence of adverse effects and positive outcomes, patient preference has rapidly increased and is still growing. The high cost still hinders the choice of emicizumab, especially in developing countries.

A rare hereditary X-linked genetic bleeding illness called hemophilia A (H.A.) is brought on by a lack of clotting factor VIII, which interferes with normal hemostasis (1,2). About 1 in 5000 male births in the U.S. is affected by H.A. (1, 3). H.A. patients often experience spontaneous bleeding episodes in their joints, which can cause long-term joint damage and consequent chronic pain, limited range of motion, and a general decline in quality of life. There is also a chance of potentially lethal cerebral hemorrhage (4).

Prophylaxis reduces long-term tissue damage at bleed sites and prevents bleeding episodes (5). Intravenous infusion of FVIII products has been a safe and successful method of replacing lost FVIII in adults and children. It can be used as an on-demand or preventative therapy (6). The prophylactic treatment of H.A. patients is suggested for emicizumabas a non-factor therapy (7–9). Regardless of FVIII inhibitors, emicizumab, a bispecific antibody, restores blood clotting by uniting factors IXa and X (7,10).

Recent studies have clarified the results of moving from FVIII to emicizumab prophylaxis in H.A. patients without

**Author for Correspondence: lollla.amen@gmail.com*

inhibitors, but numerous of these analyses were based on closed claims databases (7,1).

Building on the extensive research surrounding emicizumab, this article aims to delve deeper into its transformative role in the prophylactic treatment of hemophiliaA, particularly in overcoming the challenges associated with factor VIII inhibitors and improving patient outcomes. The article is structured to first review the molecular evolution of emicizumab, followed by an exploration of its pharmacokinetics and pharmacodynamics.

It will then examine the clinical trials that have solidified its place in hemophilia treatment before addressing the economic implications and cost-effectiveness of emicizumab therapy. The concluding sections will explore potential adverse effects and emerging clinical applications beyond hemophilia A, underscoring the broad therapeutic potential of this groundbreaking treatment.

Emicizumab evolution

The development of emicizumab as a therapeutic procoagulant is anoutcome of the pharmaceutical industry's capacity to revolutionize a molecular "linker" in tandem with an intellectual understanding of the molecular mechanisms driving thrombin generation, mediated by activated factorVIII.

Dr. Kunihiro Hattori is credited by Kitazawa and Shima with developing the idea of employing bispecific antibody to bind activated factorIX to factorX, enabling F.X. to operate as the FVIII cofactor(11). At Chugai Pharmaceutical Co., Ltd., Dr. Hattori and his team found that the distance separates the FIXa& FX-binding sites of FVIIIa on a phospholipid template is comparable to the distanceamong the human IgG 2 antigen-binding places. The age of FVIII-mimic therapy, therefore, began(12). It was an enormous and consequential task to turn the idea of FVIII mimic therapy into a workable biopharmaceutical, as Figure 1 summarizes. (13)

The development of ACE910, also known as emicizumab, resulted from testing and meticulous modification and optimization of over 2,400engineered monoclonal IgG molecules to reduce non-specific binding & immunogenicity &enhance physicochemical stability &the activity of associated activated factor VIII-cofactor.

Primate models of acquired hemophiliaA were used to produce in vivo investigations, where bleeding events had been successfully treated & prevented. These studies also provided the basis for a prophylactic procedure in hemophilia A patients, which involves weekly subcutaneous dosage.

The first human trial began in 2013 and used a single subcutaneous dose of emicizumab in healthy volunteers. It was intended to be a randomized, placebo-controlled, phaseI trial with efficacy, high bioavailability from subcutaneous administration, and no signs of hypercoagulability.

The results of weekly subcutaneous administration forstudied cases diagnosed with severe hemophiliaA over twelveyears were authorized in short- & long-term extension studies (including 12 weeks and 33.3months). Regardless of the inhibitors, the annualized bleeding rate decreased to almost zero, and four cases of non-neutralizing anti-drug antibodies did not affect treatment. (13)

Molecular basis (Bispecific Antibodies)

Bispecific antibodies mayadmit2 distinct epitopes on the same antigen or different antigens (Bs ab). They can be significant IgG-like molecules with extra domains or tiny proteins with 2 antigen-binding fragments. They bind to two different antigens sequentially or simultaneously due to physical connectivity between two binding specificities (14). By combining 2 other antigens on the same cell, bispecific antibodies can be employed to treat two different diseases (15). For every antigen-binding site, they are functionally univalent but structurally bivalent. More than 100 bs ab were reported, of which 80 are undergoing clinical studies. The US FDA has approved three of the 100 bs ab, including blinatumomab, catumaxomab, and emicizumab (16). Figure 2 shows the bispecific structure of emicizumab (11).

Mechanism of Action

Emicizumab's primary mechanism of action involves binding both FIXa and F.X., positioning both of these components in a convenient spatial location so that FIXa can activate F.X. The result of this response is comparable to the impact of being facilitated by FVIIIa. (11), as shown in Figure 2.

Hemlibra® (emicizumab) Approval

The global experience with Emicizumab has increased since it was initially approved by the European Medicine Agency & the Food & Drug Administrationin January & October 2018, respectively (17,18). Prophylaxis is now the new standard of care for hemophilia studied cases worldwide, according to the 2020Treatment Guideline issued by the World Federation of Haemophilia(19). The guideline also suggests tailored prophylaxis to provide the best possible outcomes for patients. Emicizumab's rollout has advanced quickly since its first marketing authorization in the USA and the E.U. in 2018. As

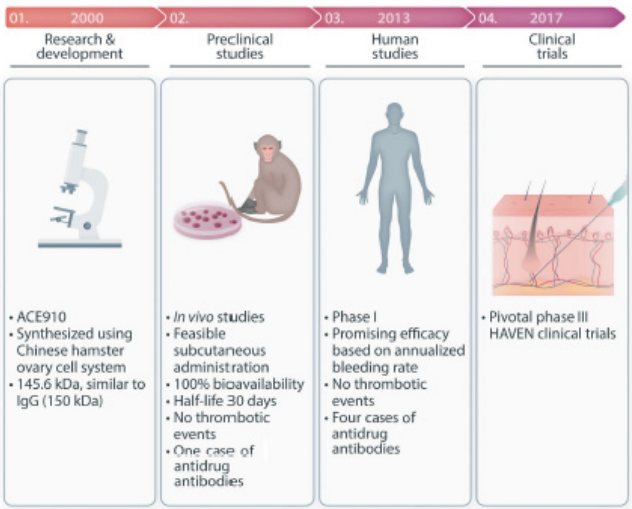

Figure 1: Development of emicizumab. (13)

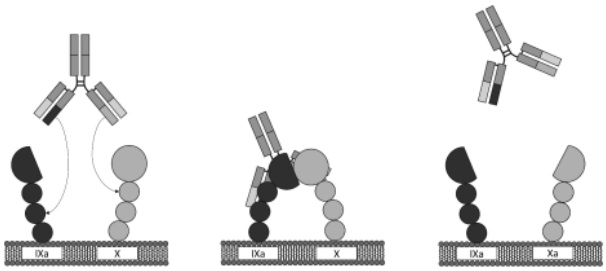

Figure 2: Diagrammatic representation of the bispecific antibody emicizumab's structure: the basis for the drug's mechanism of action (39)

of the third quarter, 107 countries had received the drug's inhibitor indication, &ninety five countries had received its non-inhibitor indication by 2021 (20).

Dose Development

The minimal concentrations of emicizumab plasma predicted to prevent bleeding in at least 50% of patients over one year were established using population pharmacokinetic modeling & simulations based on phase I & II trial data.Minimal concentrations of emicizumab plasma were applied to verify the dosing regimens formulation to be used in the pivotal phaseIII HAVEN trials: a subcutaneous loading dose of 3mg/kg administrated 1 timea week for 4weeks, followed by3different subcutaneous maintenance doses starting in week five: 1.5mg/kg once weekly, 3mg/kg once each2weeks, & 6mg/kg one time every 4weeks. All regimens' effectiveness and side-effect profiles are identical. (21).

Pharmacokinetics

Emicizumab has a favorable pharmacokinetic profile because of its relatively comfortable route of administration away from vascular access problems. The subcutaneous administration route is the attractive preference forEmicizumab treatment in hemophilia despite the absence or presence of inhibitors. Moreover, single Emicizumab administration follows a linear pharmacokinetic profile, which means it has been possible to accurately predict its serum concentration, which is relatively comparable to the dose. It has high bioavailability (eighty four percent) by subcutaneous administration&a half-life of four to five weeks in healthy adult subjects. After the first dose, achieving steady-state plasma concentration took around 12 weeks(22).

Pharmacodynamics

Emicizumab affects the blood clotting parameters in hemophilia A patients because of its modes of action. The drug's administration alters the FVIII-like activities, including prothrombin time,thrombin production,and thrombin production-activated partial thromboplastin time. Since there is essentially no baseline FVIII-like activity in PwHA, any variation in this activity is evidence of emicizumab's impact. FVIII-LA has been shown to grow and then stabilize at concentrations of more than 20 I.U./dL. Emicizumab also affects the production of thrombin (T.G.). With mean concentration values over 100nM, a rise in T.G. in PwHAis observed in the loading phase (3mg/kg/week) &affirmed in the maintenance phase (1.5mg/kg/week).

Notably, the T.G. titer was undetectable at baseline (before emicizumab was administered). Emicizumab dosing also altered PwHA's activated partial thromboplastin time. Prolonged aPTThad been seen in PwHA at baseline; however, following the first dose and during the duration of the treatment, the values stayed within normal ranges (22).Emicizumab does not stimulate the synthesis of FVIII inhibitors due to its distinct structure and sequence dissimilaritywith the FVIII structure (23). Yet, it may lead to anti-drug antibodies (ADA) creation. Emicizumab medication may also produce a highly uncommon ailment that causes ADA to build and reduces efficacy. In the HAVEN I trial, Just two of the 88 participants in Hemophilia A inhibitor-using children experienced ADAs, which led to a drop in drug concentration. Only 1studied case, however, experienced a loss of efficacy (22). The HAVEN 3 research found that PwHA without inhibitors did not develop ADA (24). Regardless of inhibitor status, emicizumab administration in a one-dosage every four weeks (Q4W) regimen did not produce ADA in PwHA (25).

The effects of ADAs on patient care could vary and, in the worst-case scenario, result in a loss of efficacy (26). The incidence of ADA against emicizumabhas been reported to be low by Schmitt et al. (26), and the drug's safety profile remains unchanged. However, more data regarding the emergence of inhibitors in Emicizumab-treated patients is required. Antiemicizumab antibodies were detected in a patient receiving this medication in a rare case reported by Harroche et al. (27). After treatment was given, spontaneous bleeding revealed the existence of ADA. These anti-Emicizumab antibody types were linked to improvingEmicizumab clearance, a sign of its induction.

This implies that aPTT and emicizumab concentrations should occasionally be measured to track the course of the treatment. The emergence of ADAs against emicizumab, which neutralizes the medication and affects clearance, was also reported by Kaneda et al. (28).

The clinical trials determining efficacy and safety

Since most people with severe H.A. now have a median yearly bleeding rate that is almost zero,attributed to successful replacement therapy of FVIII, developing neutralizing anti-FVIII inhibitors has become the most critical side effect of repeated exposure to FVIII products. 20–40% with severe H.A. and 3–13%with mild-to-moderate H.A.patientsexperience this immune response to exogenous FVIII (29), and it is linked to higher healthcare costs, morbidity, and mortality, containing a higher bleeding rate, more significant disability, & a lower quality of life(30).In the past, bypassing medicines likerecombinant activated factorVII& activated prothrombin complex concentrates were utilized to cure& prevent bleeding episodes using FVIII inhibitors. These products had sufficient hemostatic activity in actual use, but this was only momentary, difficult to sustain, and less effective than replacing FVIII in individuals who did not have inhibitors. (31)

Thus, when the HAVEN 1 & 2 clinical trials had been initiated, it was highly expected that emicizumab would be a convenient, subcutaneous, non-factor FVIIIamimic with long-lasting efficacy(32). Further research efforts aimed to expand the range of emicizumab applications, comprising of patients characterized by lack of inhibitors (HAVEN 3 and 4), originating from the Asia-Pacific area (HAVEN 5), individuals with mild to moderate H.A. (HAVEN 6), & infants (HAVEN 7)(33,34, 35).Andrade et al.(13) summarized the HAVEN clinical trials in Table 1.

The progressive outcomes of the clinical trials and the practical dosing and administration schedules have caused emicizumab's market uptake in the global H.A. treatment market to pick up speed. Since 2018, Emicizumab has been used to treat more than 12,500 patients, creatingsales of $3.6 billion in 2022 and ranked as the 34th best-selling pharmaceutical in 2022 (20,36).It is widely available in developing countries, having been distributed 2,528,730 mg to 806 patients in Latin America,Eastern Europe, Africa, and Asia,with around 64% not on inhibitors (20).

Investigation

The need for a routine laboratory test to track safety and effectiveness has grown along with the usage of emicizumab. This would provide more cost savings and customized dosing. Nevertheless, chromogenic or immunological assays are unaffected by emicizumab, but clotting-based assays are disrupted, as shown in Table 2 (24, 25).

Global coagulation testing methods have been suggested to assess emicizumab's hemostatic ability. Andrade et al. (13) summarized emicizumab interference with coagulation assays (Table 2).

Table 1: Summary of outcomes from the HAVEN clinical trials.(13)

Study	*Population*	*Doses*	*ABR median*				
HAVEN 1 2017	Adults & adolescents (≥12years old) with inhibitors	3mg/kg QW x4, followed by 1.5mg/kg QW (N=35)	2.9* (1.7-5.0)	22 (63)	2 TMA 1 CST 1 superficial thrombophlebitis	None	38
		No prophylaxis (N=18)	23.3 (12.3-43.9)	1 (6)			
HAVEN 2 2019	Children (<12 years old) with inhibitors	3mg/kg QW x4, followed by:			No TMA, no TE	4 studied cases: 2neutralizing, 2non-neutralizing	45
		1.5mg/kg QW (N=68)	0.3 (0.17-0.50)	50 (76.9)			
		3mg/kg Q2W (N=10)	0.2 (0.03-1.72)	9 (90)			
		6mg/kg Q4W (N=10)	2.2 (0.69-6.81)	6 (60)			
HAVEN 3 2018	Adults and adolescents (≥12 years old) without inhibitors	3mg/kg QW x4, followed by:			No TMA, no TE	None	33
		1.5mg/kg QW (N=36)	1.5 (0.9-2.5)	18 (50)			
		3mg/kg Q2W (N=35)	1.3 (0.8-2.3)	14 (40)			
		No prophylaxis (N=18)	38.2 (22.9-63.83)	0			
HAVEN4 2019	Adults & adolescents with or without inhibitors	3mg/kg QW x4, followed by 6mg/kg	4.5 (3.1-6.6)	23 (56)	No TMA, no TE	2 patients: 2 non-neutralizing	25
HAVEN 5 2022	Adults & adolescents (≥12years old) with or without inhibitors in Asia-Pacific region	3mg/kg QW x4, followed by:			No TMA, no TE	Eight studied cases:^ One neutralizing, Seven non-neutralizing	65
		1.5mg/kg QW (N=29)	1.0 (0.53-1.85)	19 (65.5)			
		6mg/kg Q4W (N=27)	1.0 (0.5-1.84)	15 (55.6)			
		No prophylaxis (N=14)	27 (13.29-54.91)	1 (17.1)			
HAVEN 6 2023	Adults & adolescents (≥12years old) with non-severe HA without inhibitors$	3mg/kg QW x4, followed by: 1.5mg/kg QW, 3mg/kg Q2W, or 6mg/kg Q4W (N=73)	0.9 (0.55-1.52)	48 (67)	No TMA 1 grade1 thrombosed hemorrhoid	two studied cases: Two neutralizing	34
HAVEN 7# 2022	Infants (≤12months old) without inhibitors	3mg/kg QW x4, followed by 3mg/kg Q2W (N=54)	1.9 (1.35-2.68)	23 (42.6)	No TMA, no TE	None	35

* ABR: annualized bleeding rate; 95%CI: 95% confidence interval; SAE: serious adverse events; ADA: antidrug antibodies; Ref: reference; QW: 1 time per weekly; TMA: thrombotic microangiopathy; CST: cavernous sinus thrombosis; Q2W: every 2weeks; Q4W: every 4weeks; TE: thromboembolic events.

Table 2: Interference of emicizumab with coagulation assays (13)

Influenced by emicizumab	*Not influenced by emicizumab*
aPTT aPTT-based single-factor assays: FVIII, FIX, FXI, FXII, proteinC, proteinS, APC resistance Bethesda assay (clotting based) for FVIII inhibitors Lupus anticoagulant	Chromogenic assays: FVIII (bovine substrate-based), FIX, FXI, FXII, proteinC, proteinS, anti-FXa activity triggered the clotting time Bethesda assay for FVIII inhibitors (based on bovine substrate) Prothrombin time Thrombin time Fibrinogen VWFantigen&VWF:RCo activity D-dimer Coagulation factorsGenetic tests (e.g., factorV Leiden, prothrombin20210 mutation)

aPTT: activated partial thromboplastin time; FVIII: factorVIII; FIX: factorIX; FXI: factorXI; FXII: factorXII; APC: activated proteinC; FXa: activated factorX; VWF: von Willebrand factor; RCo: ristocetin cofactor.

Adverse effects

There are occasionally adverse effects from subcutaneous emicizumab treatment, including rarely severe, clinically significant, or unrelated effects to emicizumab (37). The most frequent ones include injection site reactions (38). The HAVEN trials' most frequent adverse events& thromboembolic & thrombotic microangiopathy occurrences are shown in (Table3)(39). Because of severe bleeding when emicizumabhad been used prophylactically, patients treated with activated prothrombin complex concentrate experienced side effects like thrombosis and thrombotic microangiopathy or pulmonary embolism in patients also receiving bypassing agents (38, 40, 41). Not every additional time coagulation factor was used, thrombotic problems developed (42). Because of multiple low-grade incidents, only 1studied case in HAVEN 3 was forced to stop receiving emicizumab (43). There have been some documented fatal hemorrhages in studied cases receiving emicizumab&aPCC; however, emicizumab was not the cause of the fatalities (44). Emicizumab was used to treat an ST-elevation myocardial infarction in a studied case who had high-risk characteristics, as reported by Gundabolu et al. (40). There have been no recorded side effects that could have posed a significant risk to a patient's life in pediatric patients, suggesting that the situation is similar to that of adult patients (45). According to reports, injection site responses had been the most frequent adverse events related toemicizumab administration in the studied cases whom Young et al. studied (45). The fact that relatively few pediatric studied cases received an aPCC (46) may be consistent with this. Notably, every pediatric child tested in research by Shima et al. (46) suffered side effects from the emicizumab injection.Most often, there was a discoloration followed by excoriation and nasopharyngitis. Out of 13 individuals, there was only one injection site reaction (46). Emicizumab may cause soreness in the muscles or joints. This unfavorable outcome was reported in a male patient, age ten. Even though breakthrough bleedings are frequently linked to myalgia and arthralgia, the patient did not exhibit any of these symptoms, which suggested that the discomfort may be attributable to emicizumab. Elevated levels of emicizumab appear to be associated with discomfort in the muscles and joints (47). One particular side event was reported: three days after emicizumab was administered, observed with seven-year-old PwHA,while using inhibitors, experienced spontaneous, asymptomatic hematuria, which returned after more doses.

Ultimately, it was determined that the patient had drug-induced lupus nephritis. Emicizumab treatment had been stopped, and the studied case recovered from proteinuria, hematuria,& normalized leukocyte & lymphocyte counts (48). Our focus should be directed toward considering AHA by isolated aPTT prolongation. Female patients are not uncommon in AHA (49). Emicizumab can be used as a preventive medication after bypassing agents have been used to treat AHA patients to restore hemostatic efficacy (50). In patients with acquired hemophilia, emicizumab seldom causes side effects and aids in maintaining hemostasis (51).

Economic aspect of Emicizumab

Emicizumab's budget impact was evaluated in France, Korea, and Italy, among other previously highlighted advantages. Study teams concluded that emicizumab H.A. prophylaxis has been more cost-effective than BPA prophylaxis based on research using Markov models to examine the quality of life and cost-effectiveness between emicizumab and BPA (39).

Analysis of cost-effectiveness:

In a base-case investigation carried out over a 5-year period in France, emicizumabperformed better than BPA. A decreased frequency of spontaneous bleeding episodes also reduced hospitalization expenditures (emicizumab's ABR was lower than BPA's), resulting in savings of around 234,191 EUR per patient (38).

With the previously mentioned simplicity of emicizumab administration (subcutaneous injection), this results in a 0.88 QALY gain. Furthermore, emicizumab prophylaxis is expected to cost 6,879EUR per kg annually, while BPA is estimated to cost 15,159.90 EUR per kilogram (51).

Based on a 3-year base-case analysis, emicizumab was much more cost-effective in Italy than BPA.The estimated yearly treatment cost with emicizumabhad been 12,156,904

Table 3: Common adverse events reported in the HAVEN – studies. (39)

Common adverse effects	*HAVEN1*	*HAVEN2*	*HAVEN3*	*HAVEN4*
References	38	45	33	25
Injection site reactions	Fifteen percent	30.7percent	Twenty five percent	Twenty two percent
Headache	Twelve percent	14.8percent	Eleven percent	Twelve percent
Fatigue	Six percent	NA	NA	NA
Upper respiratory tract infections	Nine percent	23.9percent	Eleven percent	Seven percent
Arthralgia	Six percent	NA	Nineteen percent	Twenty percent
Pyrexia	NA	23.9percent	N.A.	N.A.
nasopharyngitis	NA	37.5percent	Twelve percent	Twenty seven percent

**N.A. – not assessed*

EUR, while treatment with aPCC and rFVIIa cost 32,141,369 EUR and 37,429,094 EUR, respectively. In addition to reducing treatment costs, 0.94 QALYs were gained, which enhanced patients' quality of life (52).

Emicizumab prophylaxis over BPA may result in savings of 2,612,882 USD, according to data from a base-case analysis conducted in Korea. Furthermore, patients' life expectancies were increased by 3.04 QALYs. Unlike BPA, model data indicated that PwHA receiving inhibitors on emicizumab prophylaxis experienced almost 800 fewer bleeding episodes (53).

Cost-effectiveness and side effects

Likewise, severe adverse events with low incidence associated with emicizumab—such as cutaneous necrosis, thrombotic microangiopathy, and superficial vein thrombosis, which may require hospitalization—are rare, with an occurrence rate of 6.2% (38).In contrast to twelve percent for BPA, the incidence of infusion site reactions, such as infusion site sepsis, is lower, leading to further cost reductions because of the decreased need for hospitalization (38, 51).

Clinical uses of emicizumab other than Hemophilia A

Due to its distinct procoagulant qualities and safety record, it is desirable to find out if emicizumabhelps stop or reverse bleeding caused by various coagulopathies. Yada & Nogami (54) have proposed that the procoagulant effects of increased thrombin generation by the drug may be accessible to any bleeding problem if a tiny activated factorIXamount exists to bind to emicizumab in vivo(Figure 3) (13).

Emicizumab's potential applications outside of H.A. are built on this basis, and many clinical trials have been conducted on each condition. Ogiwara et al. (55) and Chau et al.(56) concluded that Emicizumabimproved FIX activities forten-fold in mild/moderate severity H.B. wild-type FIX proteinsamples. Emicizumabtherapeutic amounts adjusted the thrombin generation deficient in vitro in samples for mild/moderate severity H.B.patients (55, 56). Minami et al.(57) studied the bispecific Emicizumab antibody affinity to factorsIX/IXa&X/Xa and found that Emicizumabdiminished the aPTT in samples of severe FXI-deficient plasma. Emicizumab slightly increased the thrombin generation potential in FXI-deficient plasma in a dose-dependent approach (57). Regarding Von Willebrand disease, spiking type3 VWD plasma with elevatedconcentrations of emicizumabextensivelyenhanced the thrombin generation assay'speak heights.Emicizumab enhanced thrombus formation under high & low shear conditions in samples from type2N studied cases(58-62).

Emicizumab was in vitro tested for its ability to reverse the therapeutic anticoagulation effects. Emicizumab was shown to shorten the aPTT in normal, non-coagulopathic plasma samples tipped with unfractionated heparinthrough in vitroinvestigations.In a pooled normal sample, Emicizumab reduced thrombin production and corrected the extended aPTT samples of plasma tampered with either argatroban (direct anti-IIa) or apixaban (direct anti-Xa)(63, 64).

CONCLUSIONS AND FUTURE RESEARCH

Emicizumab has revolutionized the treatment of hemophiliaA (H.A.), especially in patients with inhibitors, offering significant improvements over traditional FVIII replacement therapies. Its subcutaneous administration, high efficacy, and favorable safety profile have made it a cornerstone therapy. However, the emergence of anti-drug antibodies (ADAs) in a small subset of patients and challenges in clinical monitoring due to their interaction with traditional coagulation assays highlight areas that need further research.

Future work should prioritize long-term studies to estimate the safety & efficacy of emicizumab across diverse studied case populations, containing those with mild H.A. & infants. Developing personalized dosing regimens and specific diagnostic tools for monitoring emicizumab's effects will also be crucial for optimizing treatment outcomes. Expanding global access to emicizumab, particularly in low- and middle-income countries remains a key priority.Future research for adverse effects, expanding the use of the drug for other coagulopathy disorders beyond hemophilia A, has already started and is ongoing. Trials for decreasing the cost should be a target as possible. Other monoclonal antibodies and gene therapy are under investigation for helping this group of patients. Better treatment modalities will be available very soon.

Finally, exploring the potential for combination therapies and refining strategies to manage adverse effects associated with concomitant treatments will further enhance the therapeutic landscape for hemophilia A. These efforts will

ensure that emicizumab continues to improve patients' lives worldwide.

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