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Place of Emicizumab in the Management of Hemophilia A: Review Article

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ABSTRACT
Emicizumab (Hemlibra®), By connecting FIXa and FX, In hemophilia A patients, a recombinant, humanized, Absent activated factor VIII (FVIII) is successfully functionally restored by a bispecific monoclonal antibody. Subcutaneous emicizumab has been approved in a number of countries for the routine prevention of bleeding episodes in patients with moderate to severe hemophilia A, with or without the use of FVIII inhibitors. In phase III clinical investigations, emicizumab prophylaxis significantly decreased annualized bleeding rates in adults and adolescents with hemophilia A with or without inhibitors and avoided or significantly reduced bleeding in children with hemophilia A with or without inhibitors. Regular use of emicizumab improved health-related quality of life with no discomfort. Emicizumab, regardless of the presence or absence of inhibitors, provides a consistent and frequently well-tolerated alternative to conventional FVIII replacement medications for the prevention of bleeding episodes in people with hemophilia A. This is because of the delivery method's practicality and the flexible dosage schedules (maintenance doses every 1, 2, or 4 weeks).

INTRODUCTION
Emicizumab (Hemlibra®), the first non-factor replacement drug to reach the market is a subcutaneously injected, recombinant, humanized, bispecific monoclonal antibody designed to imitate the cofactor effect of activated FVIII. Emicizumab has received approval from some countries, most notably the USA and Japan, for the regular prevention of bleeding events in people with hemophilia A. regardless of whether they are also taking FVIII inhibitors. Moreover, the EU has authorized routine bleeding episode prevention in those with severe or inhibitor-dependent haemophilia A [(2)].

Emicizumab Pharmacodynamics Properties
Both FIX/FIXa and FX/FXa contain domains that are similar to epidermal growth factor are highly responsive to the humanized bispecific IgG1 antibody emicizumab [(3)]. Emicizumab reconnects To restore the function of absent activated FVIII, which is essential for effective hemostasis, activated FIX and FX in a way similar to that of active FVIII. The plasma concentration of the ternary complex and the cofactor activity of emicizumab are correlated that bridges antigens (FIX-emicizumab-FX). Emicizumab does not promote the synthesis of FVIII inhibitors since there is no sequence homology or structural similarity to FVIII [(1)].

In animal models of hemophilia A, emicizumab showed hemostatic action. For instance, In a long-term monkey model of acquired hemophilia, emicizumab prophylaxis decreased the occurrence of the spontaneous bleeding indications that were observed in the control group. A. In a model of hemophilia A blood, emicizumab increased clot stability in the presence of activated prothrombin complex concentrate (aPCC), which may assist to partially explain the elevated risk of thrombotic events when emicizumab is used and aPCC are administered together [(4)].

It has been demonstrated that emicizumab can resemble active FVIII phase I/II early trials are phase I. Emicizumab reduced the activated partial thromboplastin time and increased the peak height of thrombin generation (aPTT) in a first-in-human study including 64 healthy adult males [(5)].

Emicizumab showed mental focus pharmacodynamically reliant impact on the production of thrombin and the activity of FVIII in male hemophilia (n = 103 evaluable) Patients in the pivotal HAVEN 1 trial. After taking the first dose of emicizumab, the aPTT returned to normal (i.e., 40 s), and stayed there the entire time. A human-based FVIII chromogenic activity test showed that emicizumab treatment boosted mean FVIII activity from 1% at baseline to 30%. Prothrombin time, D-dimer, FIX and FX antigen concentrations, von Willebrand factor, or prothrombin fragment levels may change during emicizumab treatment 1.2 did not change appreciably [(6, 7)].

Pharmacokinetic Properties of Emicizumab
The pharmacokinetics of emicizumab after subcutaneous injection are dose-proportional at weekly dosages of 0.3-6 mg/kg. After giving hemophilia A patients emicizumab at a loading dose of 1 or 3 mg/kg, steady state plasma concentrations were discovered after around 12 weeks. When given once a week, emicizumab 3 mg/kg produced average trough plasma levels of 52.6 g/mL after 4 weeks of treatment. Absolute bioavailability of emicizumab after a dose of 1 mg/kg varies its median half-life of absorption is 1.6 days, ranging from 80.4 to 93.1%. [(1,6)].

Emicizumab's average apparent distribution volume is 10.4L. Emicizumab typically has an apparent half-life of around 27 days, and its average apparent clearance is 0.27 L/day. Proteolytic catabolism is the main process by

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which IgG antibodies are removed, despite the fact that the metabolism of emicizumab has not been well explored [1,2].

Phase III trials looked at the emicizumab pharmacokinetics among those with hemophilia A. The emicizumab pharmacokinetic profiles of hemophilia A patients in HAVEN 3 without inhibitors were generally comparable to those of individuals in HAVEN 1 who used inhibitors [8].

When emicizumab was given every two The pharmacokinetic profiles were generally equivalent to those after once-weekly therapy (in HAVEN 1), whether it was administered every 2 weeks (in HAVEN 2 and 3) or every four weeks (in HAVEN 2 and 4). However, when emicizumab was given every 4 weeks as compared to every 2 weeks, mean trough concentrations was lower [8].

Age (1-77 years), race (white, Asian or black), inhibitor status, mild or moderate renal impairment (creatinine clearance (CLCR) 60-89 mL/min, mild or moderate hepatic impairment (total bilirubin 1-1.5 times ULN, and any AST level), and mild to moderate renal impairment (CLCR 30 to 59 mL/min) have all been considered [1].

When given by bodyweight (mg/kg), emicizumab is exposed to patients of all bodyweight ranges, with a similar amount of apparent clearance and volume of distribution (9-156 kg) [1].

The interactions of emicizumab with other drugs have not been investigated. Clinical evidence suggests that emicizumab and aPCC may interact. If emicizumab and recombinant FVIIa or FVIII are given at the same time, hypercoagulability may result. The risk of thrombotic events should be considered when systemic anti-fibrinolytic are co-administered with aPCC or recombinant FVIIa in patients on emicizumab [2].

Emicizumab Clinical Effectiveness

Male adults, adolescents, In a series of open-label, multicenter, phase III trials, children (HAVEN 2, HOHOEMI) with hemophilia A with or without inhibitors were enrolled to look at the efficacy of subcutaneous emicizumab for the treatment of bleeding episodes were carried out. Many persons from a large non-interventional study around the world were included in the HAVEN trials [9,10,11,12].

Age 12 Years in Adults and Adolescents: Participants in HAVEN 1, 3, or 4 must have severe congenital hemophilia (HAVEN 3 and 4, 585) or congenital hemophilia A of any severity (HAVEN 1). Also, they had to have received FVIII products (HAVEN 3 and 4) or episodic or preventative bypassing drugs for at least 24 weeks previous to study admission (HAVEN 1 and 4) for at least 24 weeks [11,13].

In Patients with Inhibitors

HAVEN 1: A total of 109 patients with inhibitor-treated hemophilia A (median age 28 years), 94% of whom had severe hemophilia A, were included in HAVEN 1. Participants had already finished episodic therapy with bypassing medications. They were put into two groups, A and B, at random, and given either prophylaxis with emicizumab or none at all. Prior emicizumab prophylaxis recipients were randomized to forego agent prophylaxis (group C). Patients who had already signed up for Group D included individuals who were eligible to engage in the non-interventional trial but were unable to do so before the end of the enrolment periods for groups A, B, or C. Subcutaneous emicizumab prophylaxis was administered to patients in groups A, C, and D (3 mg/kg for the first four weeks, once each week, and then 1.5 mg/kg once per week after that). Due to insufficient follow-up at the time of data cut-off, data from group D were removed from the efficacy analysis [13].

Bleeding never happened in greater than 50% of those who had emicizumab prophylaxis. Emicizumab prophylaxis was given to patients who had participated in the non-interventional study and had a substantial decrease in the annualized bleeding rate as opposed to previous episodic (group A; n=24) or preventive therapy (group C; n=24) treatment with bypassing medicines ($P<0.0001$) reduced [14].

The prophylactic use of emicizumab enhanced health-related quality of life (HR-QoL). Teenagers (n=13) who had used prophylactic bypassing drugs in the past demonstrated numerical improvements from baseline on the domain and overall scores of the Haemo-QoL-SF, or the Hemophilia-Specific Quality of Life Assessment for Children and Adolescents. In adult patients who had previously received episodic bypassing agents, the differences in adjusted mean Hemophilia-Specific Quality of Life in Adults questionnaire (Haem-A-QoL) total and physical health domain scores at week 25 significantly (p 0.003) favored emicizumab prophylaxis versus no prophylaxis. 50–52 percent of the individuals on emicizumab prophylaxis had total Haem-A-QoL scores below 50 and 7% of the patients not receiving prophylaxis increased by more than the responder threshold (7 points) at week 25 in compared to baseline. 72% of The Haem-A-QoL physical health domain scores of emicizumab patients who had previously received preventive bypassing agents and 38% of those who had previously received episodic bypassing medicines improved as compared to baseline versus 29% of patients who did not get prophylaxis [15].

The European Quality of Life 5-Dimensions 5-Levels (EQ-5D-5L) visual analogue scale (EQ-VAS) and

the EQ-5D-5L index utility score, which assess overall health state, revealed a significant (p 0.05) connection with emicizumab prophylaxis (IUS). In contrast to 19% of patients who had not had prophylaxis, In comparison to baseline, 57% of Patients receiving emicizumab who had previously received preventive bypassing drugs or episodic bypassing medications both demonstrated gains larger than the responder criterion (+7 points), as did 33% of those patients. In contrast to 13% of patients getting no prophylaxis, 48–50% EQ-5D-5L IUS scores showed improvements from baseline that were greater than the responder criterion (+ 0.07 points) for individuals receiving emicizumab prophylaxis. With emicizumab prevention, the mean proportion of lost work days was lower than it was without it. Individuals who have already received preventive bypass surgery drugs experienced an average loss of workdays of 3% while on emicizumab prophylaxis and 9% at baseline. When emicizumab prophylaxis was administered, school absences dropped from 28% to 5%. **(15).**

STASEY: The first Results of The STASEY study, whose primary goals were to evaluate emicizumab's safety and acceptability, revealed that emicizumab prophylactic was effective in preventing hemophilia A inhibitor-related bleeding in both adults and children under the age of 12. When the data was shut off, 88 participants (3 mg/kg once weekly for 4 weeks, then 1.5 mg/kg once weekly following) had either completed the entire 24 weeks of subcutaneous emicizumab treatment or had ceased receiving it, whichever occurred first (in October 2018). 81% of patients Low annualized bleeding rates were observed, and there were no treated bleeds. Emicizumab Preference Survey results (EmiPref), the vast majority of patients (95%) indicated that they preferred emicizumab to their prior therapy, and several categories of HR-QoL and health status shown clinically significant improvements from baseline **(12).**

HAVEN 3 (Hemophilia A patients without inhibitors):

A total of 152 people included in HAVEN 3 were individuals without inhibitors who had hemophilia A (median age 38 years). After receiving episodic FVIII treatment in the past, patients were randomized to receive prophylaxis at doses of 1.5 mg once per week (group A), 3 mg every two weeks (group B), or none at all. 3 mg/kg of emicizumab was administered subcutaneously for 4 weeks, followed by 1.5 mg once a week (group B), or no prophylaxis at all (group C). Patients who had previously had FVIII prevention therapy received subcutaneous emicizumab once a week for 4 weeks, and then 1.5 mg/kg once a week (group D) **(16).**

When compared to no prophylaxis, emicizumab prophylaxis significantly decreased the rate of bleeding incidents in hemophiliac adults and children A who were not using FVIII inhibitors. Over the course of 24 weeks, emicizumab prophylaxis significantly lowered the annualized bleeding rate for treated bleeds when compared to no prophylaxis. The outcomes were substantially the same in all groups independent of age, race, how frequently a patient bled in the 24 weeks before to trial enrollment, or if a patient had target joints. Emicizumab prophylaxis significantly reduced the annualized rates of spontaneous bleeding, joint bleeding, and target joint hemorrhage when compared to no prophylaxis bleeding, and total bleeds. More than half of those who received emicizumab prophylactic never had bleeding. Intra-individual comparisons in the non-interventional study between emicizumab prophylaxis and prior FVIII prophylaxis research (group D; n=48) showed that the annualized with emicizumab prophylaxis, bleeding rate was considerably (P<0.001) decreased **(16).**

When compared to patients not receiving prophylaxis, those getting emicizumab 1.5 mg/kg At week 25, improvements were 12.5 points for once weekly and 16.0 points for 3 mg/kg every two weeks as prophylactic. By At week 25, 44% of patients receiving emicizumab prophylaxis showed a clinically meaningful change of at least 10 points from baseline in their Haem-A-QoL physical health score with 51% of patients' scores increasing at week's end 49 and 53% of patients at week 73, this improvement persisted throughout time with increases of no more than 10 points **(17).**

In the EmiPref research, the majority of participants who received emicizumab prophylaxis (94%) said they preferred the drug to their previous therapy. Reduced administration frequency, a less complicated administration route, and fewer bleeding issues were the most often cited arguments for selecting one approach over another. Emicizumab was rated as "far more" or " 90% of Patients in group D who completed the Intravenous Subcutaneous Hemophilia Injection Satisfaction Questionnaire (SQ-ISHI) found FVIII prophylaxis to be "a lot more" satisfying **(18).**

Every-four-week dosage schedule (HAVEN 4):

The outcomes of HAVEN 4, which examined the efficacy of a different emicizumab dose schedule every four weeks, confirmed those of HAVEN 1 and 3. Participants were split into a pharmacokinetic run-in group (n=7) and an expansion cohort (n=41) in this non-randomized, two-stage experiment. The expansion cohort included haemophilia A patients who had inhibitor treatment (n=5) or not (n=36) (median age, 39 years). For the first four weeks, subcutaneous emicizumab was administered once a week to all participants in the expansion cohort, a dose of 3 mg/kg was administered initially, and then every four weeks, the dose was increased to 6 mg/kg **(11).**

When given emicizumab prophylaxis once every four weeks, hemophiliac adults and kids control of clinically severe bleeding has experience. The annualized bleeding rates for treated bleeds, all treated bleeds, treated spontaneous bleeds, treated joint bleeds, as well as treated target joint bleeds, show that emicizumab prophylaxis maintained reliable bleeding control in the expansion cohort. the presence of target joints, regardless of the incidence of bleeding in the 24 weeks prior to trial participation the kind of previous therapy, or the presence of an FVIII inhibitor, annualized bleed rates were essentially constant across all established groups. Almost 50% of patients said they had no bleeding [(11)].

A preventive dose regimen of 4 weeks' worth of emicizumab was also linked to improvements in HR-QoL. The Haem-A-QoL physical health score at week 25 had a mean change from baseline of 15.41, which was higher than the responder threshold (a difference of no more than 10 points). In fact, 68% Comparable outcomes were seen at weeks and of patients reported a clinically significant Haem-A-QoL physical health score variation of 10 points between baseline and week 49 (66%) and 61 (71%) as well [(17)].

On week 25, the average percentages 1% and 3%, respectively, of lost work and school days in compared to the baseline. Every patient in the HAVEN 4 expansion group preferred emicizumab over their earlier therapy, according the results of the EmiPref survey. The top three often cited benefits of selecting were a simpler administration procedure, a reduction in administration frequency, and general improvements in HR-QoL. [(18)].

Children under the Age of Twelve with Patients' Inhibitors (HAVEN 2): Children younger more above 12 years old, taking inhibitors for their hemophilia A, and receiving subcutaneous emicizumab prophylaxis experienced significantly less or no bleeding (n=85) [(9)]. Every patient has already undergone episodic or prophylactic bypassing procedures. After receiving 3 mg/kg once weekly for 4 weeks, they were given emicizumab at dosages of 1.5 mg/kg once weekly, 3 mg/kg every 2 weeks, or 6 mg/kg every 4 weeks. The incidence of bleeding events was statistically significantly reduced as a result of emicizumab prophylaxis, with the majority of patients experiencing no bleeding. In the 1.5 mg/kg once-weekly sample of patients 12 years of age who had taken part The annualized rate of treated bleeds decreased in the non-interventional study when emicizumab prophylaxis was used in place of previous bypassing agent therapy (n=18) was reduced by 99% [(9)]. An HR-QoL survey tailored to the needs of caregivers called the Haemo-QoL-SF and Adapted InhibQoL, showed improvements in both the overall and physical health ratings, emicizumab prophylaxis was linked to numerical improvements from baseline. After week 25, 83% of patients had not missed any days of daycare or school, up from 28% at the time of the baseline visit [(19)].

Patients without Inhibitors (HOHOEMI)

It was also demonstrated that 13 Japanese children with haemophilia A under the age of 12 who lacked inhibitors responded well to subcutaneous emicizumab prophylaxis. Except for one patient, every patient had previously undergone FVIII prophylactic therapy. All patients received emicizumab at doses of 3 mg/kg once a week for 4 weeks, then at intervals of 2 mg/wkly or 6 mg/wkly. A preliminary study discovered that the use of the incidence of bleeding episodes was shown to be significantly lower when emicizumab prophylaxis was used (this study was completed after 6 patients in each dosage cohort had received 12 weeks of treatment). Patients who got 6 mg/kg every four weeks outnumbered those who received 3 mg/kg every 2 weeks, 71% to 50% did not bleed [(10)].

Operative Experience

People with hemophilia include A collective study of HAVEN 1-4 reveals that when emicizumab prophylaxis is used, minor surgical operations can be carried out safely. 19 individuals received 19 major surgical operations, while 113 others underwent 214 minor surgical procedures over the course of the four investigations (primarily dental and procedures involving devices for central venous access). Preventive coagulation factor (FVIII or bypassing agents) was not employed in 66% of minor procedures, and in 91% of those situations, there was no treated postoperative bleeding. Major procedures using prophylactic coagulation factor were performed in 84 percent of cases. One postoperative hemorrhage was controlled. No interventions led to thrombosis, unexpected bleeding, FVIII suppression, or fatalities [(20)].

Comfort with Emicizumab

Patients with hemophilia were given subcutaneous emicizumab to reduce bleeding episodes, and they generally indicated that medication was well tolerated. Results from a dosage-finding trial involving 391 male patients with hemophilia from HAVEN 1-4 and Patients who received emicizumab at least once part of standard prophylaxis are the main topics of discussion. The patient group consisted of 5 (1%), neonates between the ages of 1 month and 2 years, 50 (13%) adolescents between the ages of 12 and 18, 55 (14%) kids between the ages of 2 and 12, and 281 (72%) adults. All study participants received emicizumab treatment for a median of 34.1 weeks, with exposure periods varying from 0.1 to 224.4 weeks [(1)].

One in five people who received emicizumab suffered injection site reactions (ISRs; 22% of patients), headaches (15%), arthralgia (15%), pyrexia (6%) and diarrhea (6%), among other side events. All ISRs ranged in severity from mild to moderate, and the majority (93%) of them disappeared on their own. Some of the negative effects of emicizumab include headache, skin necrosis, superficial thrombophlebitis, thrombotic microangiopathy (TMA), and ISR. Four people (1%) quit using it as a result [(1)].

There were no new safety signals for emicizumab in the STASEY study's interim safety evaluation (median exposure duration 39 weeks), and no thrombotic events were recorded [(12)].

A pooled analysis of HAVEN 1-4 (n=400) showed that long-term emicizumab prophylaxis was still well tolerated. In this case, emicizumab exposure lasted an average of 82 weeks, albeit 77% of patients only received treatment for up to 74 weeks. No new warning signs for safety were discovered, and emicizumab was tolerated similarly to what has previously been reported [(21)].

Negative Occurrences of Special Significance

The potential for TMA and thrombosis in people taking emicizumab and aPCC together is mentioned in a (boxed warning. Patients undergoing emicizumab prophylaxis received, on a cumulative dosage on average of > 100 U/kg/day of aPCC for 24 hours before cases of TMA and thrombotic events were detected [(1)].

Three (0.8%) of the patients who received emicizumab together with aPCC had TMA. Two patients (0.5%) who had emicizum ab and thrombotic events occurred with at least one aPCC dose, neither of which necessitated the administration of an anticoagulant medication. One week following the conclusion of the aPCC, TMA showed evidence of improvement or resolution, while thrombotic events did so one month later. One TMA patient passed away, despite the fact that the detective discovered that the TMA was finished at the time of death [(13)].

The patient should be closely watched for the beginning of TMA and thrombotic events if both aPCC and emicizumab are administered to the patient at the same time. Eliminating emicizumab and aPCC at the same time is advised if there are any clinical signs of TMA or thromboembolism or if there is laboratory evidence of these conditions. When used with FVIIa or FVIII medicines, emicizumab presented no safety risks [(22)].

Emicizumab has the ability to elicit an immune response, just like other therapeutic proteins. 14 of 398 patients had anti-drug antibodies (ADAs), which were discovered (3.5%) who received emicizumab in the HAVEN 1-4 trials, including three (1%) with ADAs that may be neutralizing. After five weeks of treatment, In HAVEN 2, one patient experienced neutralizing ADAs which were linked to a reduction in emicizumab efficacy [(23)].

Dosage and administration of emicizumab

Several nations throughout the world have approved the use of subcutaneous emicizumab. It is approved for use in people (of any age) who have severe hemophilia A (congenital FVIII deficit, FVIII 1%) without inhibitors or who have mild hemophilia A (congenital FVIII deficit, FVIII 0%) for the regular prevention of bleeding episodes. In order to avoid or lessen the frequency of bleeding episodes, emicizumab is advised for routine prophylaxis in adult and pediatric patients with hemophilia A (congenital FVIII deficiency), with or without inhibitors. The Japanese individuals with or without inhibitors who have hemophilia A (congenital FVIII deficiency) frequently receive emicizumab as prophylactic to lessen bleeding tendency [(24)].

The recommended maintenance doses for emicizumab are 1.5 mg/kg 3 mg/kg every two weeks, 6 mg/kg every four weeks, or once every week. Emicizumab's suggested loading dose is 3 mg/kg once a week during the first four weeks. Based on patient compliance and the judgement of the healthcare provider, a maintenance dose should be selected. The position of each subcutaneous injection should differ from the one before it (upper arm, abdomen, or thigh). Once they have received the necessary instruction in the correct subcutaneous injection method, the patient or carer can administer emicizumab on their own (only into the abdomen or thigh). Patients under the age of seven should not administer themselves. The day before commencing emicizumab, refrain from utilizing bypassing medications as a preventative step [(1)].

Emicizumab affects clot-based assay results, including APTT stands for activated clotting time, and all aPTT-based assay outcomes. Thus, it is not recommended to utilize the results of these tests to calculate inhibitor titers, track the effects of emicizumab, or set doses for factor replacement or anticoagulation. For more information on how to administer emicizumab, as well as additional details on precautions and warnings, contraindications, interactions, and use in specific situations groups, consult your local prescription information [(1)].

Place of Emicizumab in the Management of Hemophilia A

Preventing joint injury and hemorrhage is the main objective of managing hemophilia A [(25)], preferably by substituting a clotting factor deficiency (i.e. FVIII) [(26)]. However, the short half-lives of standard FVIII replacement therapy (caused by inhibitor generation) and

the possibility of inhibitor formation limit their utilization. Although bypassing medications can be used to manage bleeding in patients who are on inhibitors, they are not the best choice for long-term prophylaxis due to their inefficiency, high cost, inconvenience, and increased risk of morbidity [(27)].

ITI therapy is the method of choice for eliminating inhibitors. Around 20–40% of patients with inhibitors are uncomfortable and/or resistant to ITI therapy, despite the fact that the majority of patients effectively gain immunological tolerance to FVIII after ITI [(28)].

The first non-factor replacement medication licensed Emicizumab, a bispecific FIXa- and FX-directed antibody developed to mimic the cofactor effect of activated FVIII, was used to prevent bleeding episodes in people with hemophilia A. Americans who are experts [(29)] and the United Kingdom [(22)] have published a consensus statement and evidence-based recommendations for giving emicizumab to patients with hemophilia A [(30)]. When hemophilia A inhibitors first became available, emicizumab was approved for the routine prevention of bleeding episodes in adult and pediatric patients [(31)].

This approval was based on findings based on findings from the HAVEN 1 and HAVEN 2 investigations, which shown that emicizumab prophylaxis significantly reduced the rate of bleeding events in adults and adolescents with hemophilia and prevented or significantly reduced bleeding in children with the illness. When compared to no prophylaxis, and inhibitors. The HAVEN 3 and HAVEN 4 studies enrolled and evaluated participants without inhibitors. The performance of emicizumab prophylaxis in hemophilia A was supported by the effectiveness of an alternate every-four-week dosing schedule. It's important to remember that HAVEN 3 examined various emicizumab dosages dosing regimens, such as once in addition to the once weekly schedule, once every two weeks and once every four weeks. Based on the results of HAVEN 3 and 4, 1.5 mg/kg once weekly of emicizumab is advised was widened to cover hemophilia A patients without inhibitors. Furthermore, new dosing schedules of 3 mg/kg 6 mg/kg every two weeks and every four weeks were added [(1)].

Hemophilia A-related psychosocial variables may significantly affect HR-QoL. Hence, the disease's effects on patients' physical and emotional well-being, discomfort and impairment, as well as their capacity for work and education, must be minimized. Empirical studies have shown that emicizumab prophylaxis enhanced HR-QoL and health status, leading to a decrease when it comes to the amount of days lost from work and school [(32)].

In clinical trials, emicizumab was often well tolerated; the most frequent adverse responses were ISRs, headaches, and arthralgia. Controlling bleeding incidents in people getting emicizumab prophylaxis who are taking inhibitors is crucial. Breakthrough bleeding patients may need further hemostatic care with bypassing drugs (such as rFVIIa, aPCC, or FVIII) [(29)].

It is important to emphasize that rFVIIa is aPCC should not be utilized before all other options have been tried as the first-line treatment for bleeding episodes. There is a specific caution concerning the likelihood of TMA and thrombosis with emicizumab for patients receiving concomitant aPCC. Individuals using emicizumab in addition to aPCC should be monitored on a regular basis to reduce this risk. TMA and thromboembolism were observed in clinical trials on emicizumab-treated patients who also received >100 U/kg/day of aPCC for 24 hours indications that the symptoms either got better or went away following aPCC removal. Giving FVIIa or FVIII products at the same time seems safe to people on emicizumab prophylaxis [(30)].

Emicizumab affects every clot-based assay, making it challenging to correctly assess FVIII activity and inhibitor titers [(33)]. As emicizumab has a long half-life, this interference may endure for as long as six months following the last dose [(1)].

Hence, it may be difficult to monitor FVIII activity and inhibitor titers when treated with emicizumab (for instance, in situations where there has been breakthrough bleeding or extensive surgery) [(33)].

Several techniques have been developed to assess FVIII activity and inhibitor titers during emicizumab prophylaxis. However, human chromogenic assays can be used to evaluate emicizumab activity while bovine chromogenic assays FVIII activity and inhibitor titers can be determined using this method. In these circumstances, one-stage clotting assays are unsuccessful [(34)].

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