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Bispecific Antibodies and Advances in Non–Gene Therapy Options in Hemophilia

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Abstract

Regular prophylaxis has markedly improved the treatment for patients with hemophilia A, especially after the introduction of highly purified factor VIII (FVIII) concentrates. However, frequent intravenous infusions and the development of FVIII inhibitors remain as unsolved difficulties. To overcome these unmet needs, a bispecific antibody mimicking activated FVIII has been developed in Japan. This bispecific antibody, emicizumab, recognizes activated factor IX (FIXa) and activated factor X (FXa), and promotes FIXa-catalyzed activation of FX in the absence of FVIII. Emicizumab initially reacts with FIXa generated by the action of factor VIIa/tissue factor complexes. Subsequently, thrombin generation is enhanced in the presence of higher amounts of FIXa derived from FXIa-dependent mechanisms. Hence, emicizumab-driven FXa and thrombin generation is maintained by a FXI activation loop in the intrinsic coagulation pathway. Reactions downstream of emicizumab are regulated by natural anticoagulants including activated protein C, antithrombin, and tissue factor pathway inhibitor. Phase 3 studies (HAVEN 1-4 and HOHOEMI studies) demonstrated a remarkable reduction in bleeding rates together with a high percentage of patients with zero treated bleeds irrespective of the presence of inhibitors. In general, emicizumab proved to be well tolerated, although isolated thromboembolic and thrombotic microangiopathic complications were observed in the HAVEN 1 studies, and 3 out of a total of 400 patients developed neutralizing antidrug antibodies. In addition, several questions remain to be discussed with respect to open-use clinical practice, including when to start treatment, how to monitor therapy, and optimum dosage for surgical procedures and immune tolerance induction.

KEYWORDS

bispecific antibodies, emicizumab, factor VIII prophylaxis, hemophilia A therapy

Essentials

- Bispecific antibody, emicizumab, recognizes activated factor IX (FIXa) and activated factor X (FXa), and promotes FIXa-catalyzed activation of FX in the absence of factor VIII.
- Phase 3 studies demonstrated reduced bleeding rates irrespective of the inhibitor.
- Emicizumab is well tolerated, although isolated thromboembolic and thrombotic microangiopathic complications may occur.
- Remaining questions include when to start, monitoring, supplementary hemostatic treatment and immune tolerance induction.

1 | INTRODUCTION

Hemophilia A is the most common of the severe congenital coagulopathies, attributed to quantitative and qualitative deficiencies of factor VIII (FVIII), and characterized by various types of recurrent bleeding. Patients with hemophilia A are classified into 3 subtypes based on diagnostic levels of FVIII activity (FVIII:C), including severe (FVIII:C < 1 IU/dL), moderate (1-5 IU/dL) and mild (>5-40 IU/dL).[1] The main principles for the current treatment of patients with hemophilia A depend on regular prophylaxis using FVIII concentrates,[2-4] and the gold standard is 3 times a week or every other day to maintain plasma FVIII trough levels over 1-3 IU/dL. Recently, new recombinant FVIII products with an extended half-life (EHL) have made it possible to reduce the frequency of treatment to twice a week or every 3-5 days.[5,6] Several unmet needs remain in the current prophylactic protocols for patients with hemophilia A, however. The requirement for frequent intravenous intervention presents a heavy burden, especially in pediatric and older patients who need support from caregivers for infusion. Also, the development of neutralizing FVIII inhibitors, which diminish or substantially reduce the effect of FVIII, and difficulties in maintaining adequate hemostatic level of FVIII especially in physically active patients, can be serious issues. Furthermore, several reports have indicated that it is very difficult to completely protect from hemarthrosis using current regimens, even starting in early childhood.[7] To circumvent these difficulties, nonclotting factor concentrates have been developed, including bispecific antibody, RNA interference therapy that targets antithrombin[8] and anti–tissue factor pathway inhibitor (TFPI) monoclonal antibodies.[9] In this context, the bispecific antibody, emicizumab, which mimics the procoagulant function of activated FVIII (FVIIIa) has been approved in over 60 countries and now offers an effective option for prophylactic treatment for patients with hemophilia A irrespective of the presence of inhibitors. The efficacy of emicizumab in clinical trials was excellent, and tolerable safety was confirmed, although some adverse events, including thromboembolic TMA and neutralizing antidrug antibodies (ADAs) were reported in specific circumstances.[10] More recently, however, several questions have become apparent for the clinical use of emicizumab. In this review, the development of emicizumab is summarized, the potential uses of the antibody in wider clinical settings are discussed, including the availability of postmarketing data, and selected abstracts presented at the 2019 International Society on Thrombosis and Haemostasis (ISTH) Congress reviewed.

2 | PRECLINICAL DEVELOPMENT OF EMICIZUMAB

FVIII is transformed to FVIIIa by thrombin and FXa. This procoagulant protein functions as an essential cofactor in the factor IXa (FIXa) catalyzed activation of FX.[11] The concept of emicizumab was based on the hypothesis that FVIIIa supports suitable interactions between the active site of FIXa and the FX substrate site by localizing the catalytic center of FIXa at the FX cleavage site. Furthermore, the distance between FIXa- and FX-binding sites is similar to that between the 2 antigen-binding sites of human IgG. Therefore, a bispecific antibody recognizing FIXa with 1 arm and with FX with the other arm at a suitable distance and angle, could exert FVIIIa cofactor function and help maintain adequate trough levels of coagulation activity. The development emicizumab began about the year 2000 in Japan.[12] Initially, 20 anti-FIXa and 23 anti-FX monoclonal antibodies were produced in mice by immunization with human FIXa or FX. Genes of the variable regions of these antibodies were inserted into an expression vector containing the constant region of human IgG, and were used to generate a total of 430 bispecific IgG products in human embryonic kidney (HEK) cells. The first prototype bispecific antibody, mediating a shortening effect on the prolonged activated partial thromboplastin time (APTT) in FVIII deficient plasma, was obtained from these antibody clones. In vivo experiments were not successful, however. Subsequently, therefore, approximately 200 monoclonal antibodies against FIXa and 200 antibodies against factor X (FX) were produced from mice, rats, and rabbits to increase the choice of antibodies with distinct molecular characteristics. One promising bispecific antibody, denominated hBS23, was obtained from a total of 40 000 bispecific IgG combinations in HEK, and hemostatic effects were confirmed using a primate model of acquired hemophilia A, developed by infusing neutralizing anti-FVIII antibodies.[13] After further optimization, a final version of this bispecific antibody, ACE 910, was obtained.[14]

Emicizumab activity is dependent on the exposure of phosphatidylserine on phospholipid membranes, indicating that the antibody would not function in normal circulating blood.[15] Although emicizumab mimics FVIIIa procoagulant activity, its kinetic profile is different from that of native FVIIIa. The binding affinities to FIX/FIXa (KD values:1.58/1.52 μM) and FX/FXa (1.85/0.978 μM) are weaker compared with other antibody drugs,[15] and this low binding profile allows the release of FXa from emicizumab easily

leading to subsequent prothrombinase reaction. Kinetic experiments of FIXa catalyzed FX activation demonstrated a 43.8-fold slower rate of activation compared to FVIIIa.[15] Emicizumab does not inhibit the regulatory effect of TFPI and antithrombin.[16] Furthermore, emicizumab-driven thrombin generation is downregulated by activated protein C through inactivation of activated factor V.[17] These in vitro data indicated that emicizumab procoagulant activity can be regulated by the natural anticoagulation system.

At sites of bleeding, FIXa is initially generated by FVIIa/tissue factor, and emicizumab binds to both FIXa and FX inducing FXa generation in the early (extrinsic) stages of the coagulation mechanism (Figure 1A). Consequently, the action of emicizumab is much faster than that of FVIII, which requires activation by thrombin. Subsequently, emicizumab-driven FXa generation is propagated by FIXa produced by thrombin-activated FXIa in the intrinsic coagulation reaction (Figure 1B). Moreover, extrinsic FIXa might be inhibited by TFPI, and emicizumab potential is maintained by the intrinsic FIXa activation loop. Furthermore, emicizumab-induced generation of FXa in the absence of FXIa is much lower than that in its presence, and optimum emicizumab potential appears, therefore, to depend on FIXa derived from intrinsic FXIa.[18]

3 | SUMMARY OF CLINICAL TRIALS

Safety and pharmacokinetic and pharmacodynamic properties of emciczumab were evaluated in phase 1 studies of healthy adults using single subcutaneous injections of ACE 910 in a dose escalation manner.[19] Exploratory phase 1 studies were also commenced for assessing prophylactic efficacy in patients with hemophilia A with and without inhibitors by weekly subcutaneous injections in 3 dose cohorts: 0.3, 1.0, and 3.0 mg/kg.[20] The calculated annual bleeding rates (ABRs) were markedly reduced, and in an extended study[21] the prophylactic effect was maintained for over 2 years without drug-related serious adverse events (SAEs). On the basis of these data, dosing regimens were simulated for phase 3 studies.[22] The concept of emicizumab prophylaxis is to maintain plasma concentrations at 45-50 μg/mL, equivalent to 13%-15% FVIII activity,[13] at which levels it should be possible to achieve a zero treated bleeding rate.[23] Hence, in accordance with the model simulations, 3 dosing regimens were determined; weekly injections at 1.5 mg/kg, 3.0 mg/kg every 2 weeks, and 6.0 mg/kg injection every 4 weeks . The results of these phase 3 studies[24-27] are summarized in Table 1.

In general, a remarkable reduction in treated ABR was confirmed in all 3 dosing groups, irrespective of the presence of a FVIII inhibitor. Furthermore, the percentage of patients with

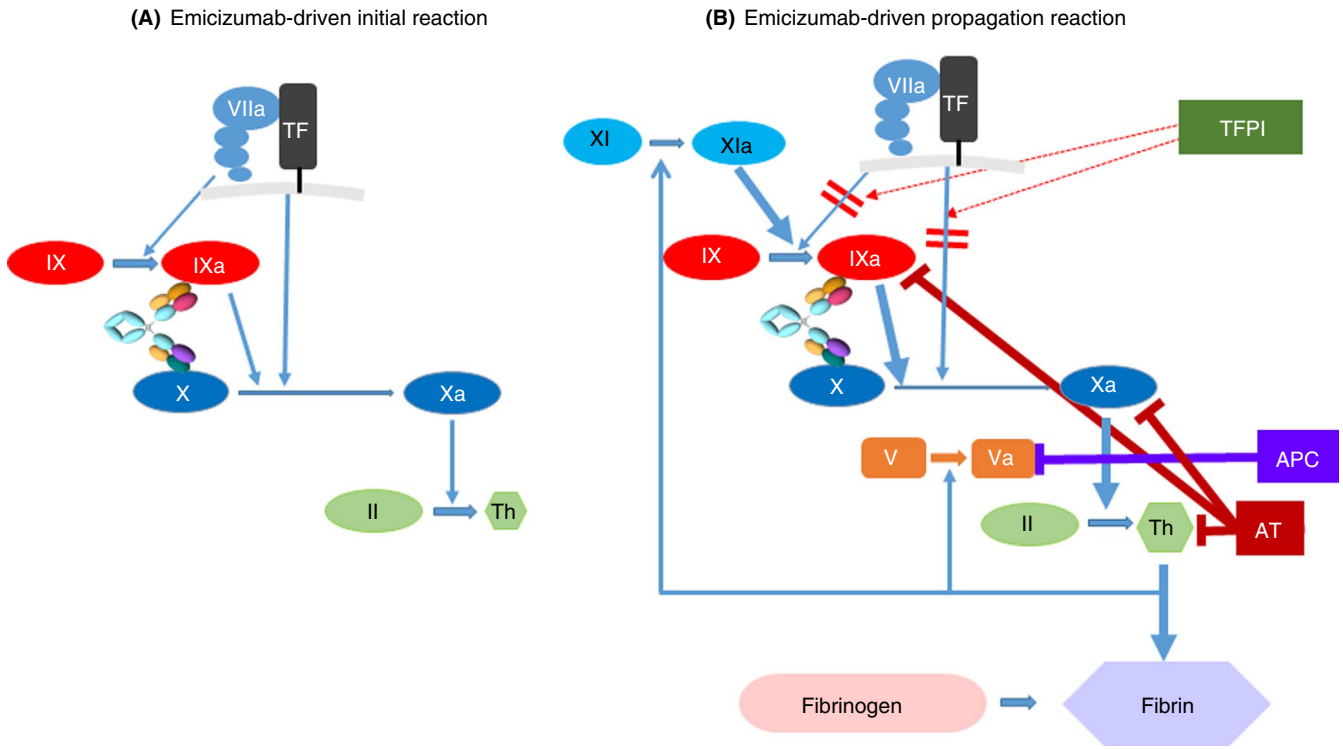

FIGURE 1 Mode of action of emicizumab in the coagulation system. Emicizumab initially reacts with factor IXa (FIXa) mediated by the factor VIIa (FVIIa)/tissue factor complex (A). Under physiologic conditions, FVIIa/tissue factor activity is limited by tissue factor pathway inhibitor (TFPI). Emicizumab-driven factor Xa (FXa) and thrombin generation is enhanced, however, in the presence of factor IXa (FIXa) derived from FXIa-dependent reactions. Hence, FIXa is supplied through a factor XI (FXI) activation loop, and emicizumab-driven FXa and thrombin generation is maintained (B). Reactions downstream of emicizumab are regulated by natural anticoagulants including activated protein C (APC), antithrombin (AT), and TFPI

TABLE 1 Summary of the results of phase 3 HAVEN studies

Emicizumab clinical trials	Eligible patients	Prior treatment	Number of patients	Emicizumab dosing	ABR (% reduction vs ref arm)	Patients with no treated bleeds (%)	safety
HAVEN 1[24] (NCT02622321)	Inhibitor patients (age ≥ 12) (N = 113)	OD	35	QW	2.9	62.9	2 TEs/3 TMAs 1 ADA
		OD	18	Control arm	23.3	5.6	
		Px	49	QW	5.1	69.4	
HAVEN 2 [25] (NCT02795767)	Paediatric inhibitor patients (age 0-11) (N = 88)	Px and OD	68	QW	0.3	76.9	No TE/ TMA 2 ADAs
			10	Q2W	0.2	90	
			10	Q4W	2.2	60	
HAVEN 3 [26](NCT02847637)	Noninhibitor patients (age ≥ 12) (N = 152)	OD	36	QW	1.5	55.6	No TE/ TMA
		OD	35	Q2W	1.3	60	
		OD	18	Control arm	38.2	0	
		Px	63	QW	1.5 (68% reduction)	55.6	
HAVEN 4 [27] (NCT03020160)	Inhibitor and noninhibitor patients (age ≥ 12) (N = 48)	Px and OD	48	Q4W	2.4	62.9	No TE/ TMA

Abbreviations: ABR, annual bleeding rate; OD, on demand; Px, prophylaxis; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; TE, thromboembolic event; TMA, thrombotic microangiopathy.

zero treated bleeds was approximately 60%. Adverse events (AEs) mostly included local skin reactions at injection sites. In the HAVEN 1 study,[24] however, 2 patients with FVIII inhibitors reported thromboembolic events (TEs), and 3 developed thrombotic microangiopathy (TMA). In each of these cases, higher or repeated doses of activated prothrombin complex concentrates (APCCs) had been infused for breakthrough bleeding. No patients treated with supplementary recombinant FVIIa (rFVIIa) alone developed TE or TMA. Consequently, rFVIIa has been recommended as first-line therapy for breakthrough bleeding during emicizumab prophylaxis. The occurrence of ADAs has also been identified as a rare SAE, including 2 pediatric patients who developed neutralizing ADAs in the HAVEN 2 studies.[25] The frequency of ADAs in these circumstances appears to be low compared to that reported with other antibody drugs. Nevertheless, the findings indicated that ADAs as well as TE/TMA should be carefully assessed during the emicizumab prophylaxis. The pathogenesis of TMAs in these circumstances is not known with certainty, although APCC contains significant amounts of FIXa and FX, and the adverse TEs may be related to enhanced thrombin generation. There are no reports to date, however, of TEs/TMAs in noninhibitor or pediatric patients. More recently, longer-term safety and efficacy over a 96-week follow-up period in 400 patients who participated the HAVEN studies was reported at the latest congress of the ISTH.[28] There were no further drug-related AEs. Furthermore, treated ABRs over consecutive 24-week treatment intervals decreased, and the proportion of participants with no or 1-3 treated bleeds increased over time. At weeks 73-96, the rate of zero treated bleeding was 88.6%.

4 | QUESTIONS FOR THE WIDER USE OF EMICIZUMAB IN THE POSTMARKETING ERA

In general, the results of the phase 3 studies were promising and demonstrated that emicizuzmab offers a substantial new treatment option for the treatment of patients with hemophilia A regardless of the presence of FVIII inhibitors. Emicizumab has been now been approved in over 60 countries, and the number of patients with hemophilia A undergoing emicizumab prophylaxis is increasing. Nevertheless, several questions and concerns are emerging regarding the universal use of emicizumab in open clinical management of patients with hemophilia A (Figure 2).

4.1 | The challenge of monitoring therapy

Monitoring antibody activity appears to be an important practical aspect during emicizumab prophylaxis, and there may be several clinical circumstances in which monitoring would be required. The relationship between procoagulant activity and plasma concentration of emicizumab remains to be fully established, however. The unique mode of action of emicizumab mimicking FVIIIa precludes the use of standard APTT coagulation techniques including APTT-based FVIII activity assays,[10,12] and other available options should be considered. For example, measurements of FVIII-equivalent activity may be calculated from circulating antibody concentration using the value of 0.3 IU/mL/μg/kg defined using the in vivo simulation primate model of acquired hemophilia A.[13] In addition,

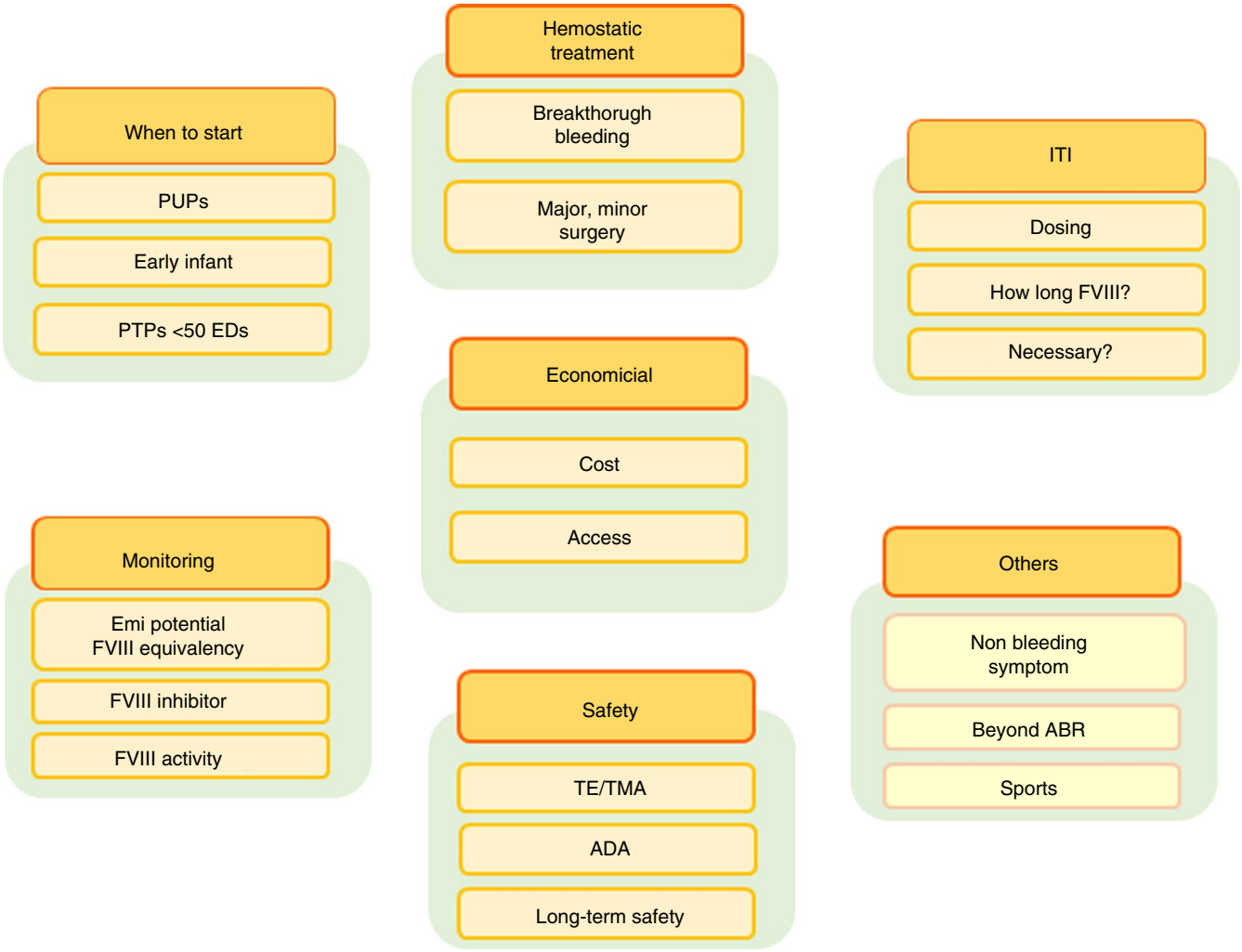

FIGURE 2 Questions regarding the open use of emicizumab prophylaxis in clinical practice. Questions regarding the general use of emicizumab in clinical practice after regulatory approval are discussed above and can be grouped under convenient headings. Figure 2 outlines the key points that deserve consideration at various time points before and during therapy

a modified APTT-based assay using a calibrator of diluted emicizumab mixed with FVIII-deficient plasma was described at the recent ISTH meeting.[29] This assay is similar to the current 1-stage clotting method used for measurements of chromogenic FVIII (FVIII:C) and appeared to be insensitive to endogenous interferents. Alternatively, since emicizumab reacts only with human and primate FIXa and FX, chromogenic assays using human reagents may be useful to some extent.

Moreover, modern assays to assess global or comprehensive coagulation function could be particularly informative. For example, we have demonstrated that a modified clot waveform analysis technique using a mixed APTT and prothrombin time reagent offered advantages for evaluating emicizumab potential.[30] In this assay, maximum coagulation velocity correlated well with the concentration of emicizumab. Similarly, rotational thromboelastometry (ROTEM) and thrombin generation assays could provide valuable data for monitoring emicizumab activity.[31-33] Nonactivated ROTEM without the addition of APTT or PTT reagents could be especially informative and may be the simplest method for monitoring emicizumab therapy.[31]

Monitoring FVIII activity or FVIII inhibitor levels may also be essential during intensive hemostatic treatment for breakthrough bleeding or surgical interventions. As mentioned above, emicizumab interacts only with human and primate FIXa/FX, and therefore chromogenic assays using bovine reagents could be helpful in these circumstances. Another option could be the use of anti-idiotype monoclonal antibodies against emicizumab.[34] Emicizumab activity is completely neutralized by anti-FIX(a) and FX(a) Fab antibodies. Hence, standard APTT-based FVIII and FVIII inhibitor assays may be reliable after neutralization with these antibodies. Furthermore, this type of assay is applicable to measurements of other clotting factors and natural inhibitors including protein C/protein S and antiphospholipid antibodies.

Finally, the detection and monitoring of anti-emicizumab antibodies could have serious implications for therapeutic effectiveness. Although the immunogenicity of emicizumab is minimized by several optimization procedures based on in silico analysis during manufacture, the development of ADAs remains a risk. Two pediatric cases out of a total of 400 patients who participated in the HAVEN studies developed neutralizing ADAs. Although the APTT is not useful for

assessing FVIII-related emicizumab activity, it may help to detect the presence of ADAs due to its high sensitivity to the biphasic antibody. Circulating emicizumab concentrations are generally decreased after the development of neutralizing ADAs, and consequently the shortening effects of emcicizumab on the APTT is reversed. Hence, APTT-based assays for antibody concentration discussed above could be useful for predicting the occurrence of ADA.

4.2 | Supplementary hemostatic treatment during emicizumab prophylaxis

Additional hemostatic therapeutics may be required during emicizumab prophylaxis, especially with traumatic breakthrough bleeding or during surgical procedures. Some patients with hemophilia A with inhibitors in the HAVEN 1 study developed thrombosis and TMA after supplementary treatment with APCC at doses averaging more than 100 μg/kg daily for >1 day. No thrombotic events were reported in patients treated with APCC for 1 day or with rFVIIa alone.[24] Guidance from the National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) in the United States recommends, therefore, that the concomitant use of APCC with emicizumab is avoided if possible or limited to <50 μ/kg as an initial dose and for <1 day.[35] Conclusive information and evidence to support optimal dosing of bypassing agents (BPAs) in conjunction with emicizumab is lacking, however. In vitro and ex vivo studies have demonstrated that thrombin generation is accelerated by APCC at much lower doses in the presence of emiciumab, and that APCC demonstrates synergistic potential in combination with emicizumab. In contrast, the action of rFVIIa appears to be additive, and Seaman recently reported successful major orthopedic surgery for hip arthroplasty in a patient treated with rFVIIa during emicizumab prophylaxis. In this case, 180 μg/kg rFVIIa was infused preoperatively and 90 μg/kg of rFVIIa was infused every 3 hours for 4 days. This was followed by reducing doses to every 6 hours for an additional 4 days, every 8 hours for 4 days, and then every 12 hours for a further 3 days.[36] Moreover, an update of all 4 HAVEN studies in 400 patients included a total of 215 cases of minor surgery. The summary was reported at the recent ISTH congress[37] and demonstrated that 141 procedures (65%) were performed without the use of prophylactic hemostatic therapeutics, and 121 (91%) were successful without additional treatment. Furthermore, major surgery has been reported in another 18 patients. Three of these cases were managed only with emicizumab prophylaxis, and no postoperative bleeding occurred. Fifteen cases were treated with additional clotting factor concentrates including FVIII or BPAs. In 12 of these, no postoperative bleeding occurred, and only 1 patient required hemostatic treatment. The other 2 cases did not require additional therapy.

4.3 | Impact on treatment for hemophilia A patients with inhibitors

The best targeted subjects for emicizumab prophylaxis are hemophilia A patients with inhibitors. HAVEN 1 and 2 studies demonstrated a remarkable reduction in treated ABR in this group of individuals. Again, however, several therapeutic options can be considered, especially when the inhibitor is first detected.[38] A higher mortality rate is observed in these patients than in noninhibitor patients, and there is an enhanced risk of thrombotic events with the intensive use of bypassing products for severe bleeding or major surgery. In addition, the potential for gene therapy is limited in these individuals. Immune tolerance induction (ITI), therefore, remains a pivotal treatment for eradication of inhibitor. However, the clinical trials of emicizumab discussed above have demonstrated marked reductions in bleeding frequency, a better clinical outcome, and an improvement of quality of life not only for patients but for caregivers, suggesting that starting emicizumab prophylaxis independent of ITI could be an effective alternative.[39] The use of emcicizumab coupled with ITI could also be considered, although several uncertainties should be addressed, including dosing regimens; the management of thrombotic risk or safety, especially for breakthrough bleeding; and maintenance treatment after successful ITI.[40]

Recently, Batsuli et al[41] described the Atlanta protocol and presented preliminary data for ITI in pediatric patients with hemophilia A with inhibitor treated with emicizumab. Eight patients with an inhibitor titer of 2.0-198 BU/mL participated this study. Five patients received 100 IU/kg standard rFVIII 3 times a week. One patient received EHL rfVIII Fc fusion protein at 100 IU/kg, and another patient received the same fusion product at 50 IU/kg 3 times a week. The other patient was treated with plasma-derived FVIII at 50 IU/kg 3 times weekly. In general, the dosing was medium between standard high- and low-dose protocols.[42] Four patients had recently commenced ITI. The other 4 patients (patients 1, 2, 4, and 5) had been treated with emicizumab and ITI for a median duration of 15 weeks (range, 13-18 weeks). All inhibitor titers declined, and no anamnestic response were observed. The inhibitor titers before ITI and at the last measurements were 0.7-30.7 and 0.3-3.7 BU/mL, respectively. Furthermore, none of the patients developed thrombosis or TMA. These early data suggested that ITI can be performed accompanied with emicizumab prophylaxis without safety concerns. In this context, Carcao et al[43] from the Future of Immunotolerance Treatment (FIT) Study Group discussed ITI in the modern era of nonfactor therapies. They proposed starting FVIII at a low dose (50 IU/kg) and low frequency (3 times weekly) escalating to 200 IU/kg daily if the inhibitor titer rises. As noted above, however, MASAC recommended the use of no more than 50 IU/kg per dose of FVIII[35] in view of the thrombotic risks associated with BPAs used for breakthrough hemorrhage.

No information is available to recommend or suggest the optimum duration of maintenance treatment after successful ITI. Antun et al[44] reported the results from a multicenter retrospective cohort study on relapse after successful ITI. In this study, a total of 64 cases of hemophilia A with FVIII levels <2 IU/dL who were considered successfully tolerant following ITI were investigated for inhibitor recurrence. The probability of any recurrent inhibitor at 1 and 5 years was 12.8% and 32.5%, respectively. Multivariable analysis led to the conclusion that adherence to post-ITI prophylactic FVIII infusions is not a major determinant of recurrence.

Nevertheless, given the limited information and experience in this field, it is difficult to define precise maintenance treatment. The FIT study group recommended continued regular infusions of FVIII once or twice a week for at least 6 months after ITI success.[43] Furthermore, emicizumab alone may be an option, considering the marked reduction in ABR, the burden of frequent FVIII infusions, and catheter-related thrombotic and infection risks. Therefore, further clinical studies on ITI and emicizumab are essential. In the meantime, decisions on various treatment options including ITI at first detection of inhibitor should remain based on individually informed patient consent.

4.4 | Impact on treatment for noninhibitor patients with hemophilia A

When to start treatment and what defines suitable patients are both important practical aspects for emicizumab therapy. The current gold standard treatment for noninhibitor patients with hemophilia A is regular prophylaxis with FVIII concentrates starting in early childhood. A pioneering, randomized controlled clinical investigation by the Joint Outcome Study (JOS) demonstrated that regular prophylaxis starting before 30 months leads to better joint outcome at the age of 6 years than episodic treatment.[4] In the JOS continuation study, the proportions of participants in the early prophylaxis and episodic/late prophylaxis groups at the age of 6 years were 93% and 58%, respectively, and interim analysis has indicated that at the age of 18 years the zero-percentage index of osteochondral damage, assessed by magnetic resonance imaging (MRI) or the need for joint surgery, in the early prophylaxis and episodic groups was 67% and 24%, respectively.[45] These results confirmed that initiation of regular prophylaxis in the toddler years is critical to protection from joint damage. Nevertheless, significant joint damage was still observed in 33% of the patients in the early prophylaxis group at the age of 18 years. Nijdam et al[46] described a retrospective single-center cohort comparison of the long-term effects of age at starting prophylaxis and the number of joint bleeds before starting prophylaxis. They demonstrated a significant difference in Predicted Pettersson score between patients starting prophylaxis before joint bleeding and other groups with ≥1 bleed before prophylaxis. Furthermore, image analysis of joints by MRI and ultrasound revealed pathological changes due to nonsymptomatic subclinical hemarthroses.

Intracranial bleeding (ICH) is another vital consideration for early prophylaxis. ICH is the most serious event that can occur in people with hemophilia, resulting in high rates of mortality and severe physical and mental disability. A literature review of the past 20 years revealed that ICH is more frequent in childhood, especially at <2 years old, and in adults >60 years old with other known risk factors including hypertension.[47] The data highlight that in spite of current prophylactic protocols starting at toddler age, the risk of ICH exists in young neonates until the establishment of regular prophylaxis.

At present, clinical experience with noninhibitor pediatric patients receiving emicizumab prophylaxis is available from only a small number of centers. We have recently reported the interim results from a multicenter open-label phase 3 study of pediatric noninhibitor patients <12 years old treated with emicizumab every 2 and 4 weeks.[48] In this study, the median age of participants was 6.6 years (1.5-10.7) in the every 2 weeks cohort and 4.1 years (0.3-8.1) in the every 4 weeks cohort. Three patients were <2 years old, including 1 previously untreated patient. The treated ABR and zero treated bleeding indices in the every 2 weeks cohort were 1.3 (95% confidence interval [CI], 0.6-2.9), and 33.3%, respectively. The comparative figures in the every 4 weeks cohort were 0.7 (95% CI, 0.2-2.6) and 71.4%, respectively. These findings were similar to those of other HAVEN studies. There were no thrombotic complications, TMAs, or serious drug-related AEs. Nevertheless, although there have been no reports of thrombosis or TMAs in noninhibitor adults or children in the HAVEN 3 and HAVEN 4 studies, long-term safety requires careful observation in wider clinical practice.

Several concerns remain regarding early emicizumab prophylaxis, however. Long-term safety of emicizumab, especially in pediatric patients, is unknown. Hepatic synthesis of vitamin K–dependent clotting factors remains immature for several months after birth. Hence, the levels of natural anticoagulants including protein C, protein S, and antithrombin are reduced, and the balanced regulation of coagulation in the neonatal and early infant period may be different from that in older pediatric patients. Also, it is important to keep in mind that there is still a risk of inhibitor development during emicizumab prophylaxis due to concomitant FVIII administration for breakthrough bleeding or surgical intervention within 50 exposure days.

The other expected benefit of emicizumab prophylaxis is protection from subclinical bleeding. The presence of subclinical bleeding was demonstrated by MRI in some pediatric patients in the JOS report,[4] and this may be one reason for the difficulties related to complete protection from joint damage using the current standard early prophylaxis regimens. Furthermore, more importantly, there is a substantial risk of underestimating the effects of untreated joint bleeding due to the short half-life of FVIII and lower trough levels of procoagulant activity during current standard prophylaxis. In this context, therefore, it could be expected that the pharmacokinetic profile of emicizumab would help to maintain higher trough levels of FVIII equivalent activity, leading to a positive effect on protection from subclinical bleeding and improved joint health. Although there is no evidence to support these effects by emicizumab prophylaxis, several clinical studies are ongoing to explore musculoskeletal assessment with MRI and ultrasound examination.[49,50]

The overall evidence from the different clinical trials suggests that the advantages of emicizumab prophylaxis, including subcutaneous access, higher trough levels based on the FVIII equivalent activity, a longer half-life than EHL rFVIII, and no direct risk of inhibitor development, could help to solve the limitations of current prophylactic regimens, especially soon after diagnosis or in previously untreated patients. More recently, clinical trials of other nonclotting factors including RNA interference therapy that targets antithrombin[8] and

anti-TFPI antibodies (concizumab)[9] are ongoing or are about to start, and patients with hemophilia A that have developed anti-emicizumab antibodies and anti-FVIII inhibitor may be especially suitable candidates for these other nonclotting factor concentrates.

4.5 | Safety issues in postmarketing clinical settings

A total of 9 serious thrombotic events have been identified in postmarketing records (data cutoff December 31, 2019).[51] Treatment in these patients included concomitant use of other hemophilia medication including APCC at concentrations not exceeding the cumulative dose stipulated in the box warning notice from the US Food and Drug Administration. (doses >100 units/kg/day for 24 hours or longer). In addition, 17 cases of death have been listed in this postmarketing surveillance.[51] Detailed information of each case is restricted, however, and it is difficult to know whether these thrombotic events and fatalities are drug related or not. Furthermore, >6000 patients have now been treated with emicizumab. Nevertheless, continuous careful observation during emicizumab prophylaxis and thorough postmarketing information will be essential, as with any new treatment product.[52,53]

In conclusion, the FVIIIa-mimicking bispecific antibody, emicizumab, has introduced the potential for substantial improvements in quality of life for patients with hemophilia A of all ages, regardless of the presence of FVIII inhibitors. Questions regarding the wider application of emicizumab therapy require longer-term observations, essentially including well-controlled postmarketing clinical studies.

RELATIONSHIP DISCLOSURE

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