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REVIEW ARTICLE

VIA MEDICA

Emicizumab in severe hemophilia A

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Abstract

Emicizumab is a recombinant, humanized, bispecific, asymmetric monoclonal antibody that bridges activated factor IX and factor X (FX) and leads to activation of FX, thus mimicking the hemostatic function of activated factor VIII (FVIIIa).

The clinical trial program showed that emicizumab prophylaxis maintains low bleed rates and is well tolerated by patients with hemophilia A of all ages with and without factor VIII (FVIII) inhibitors. Emicizumab prophylaxis in severe hemophilia A patients with high titer inhibitor against FVIII was launched in Poland in 2020. As of April 2021, 42 patients were receiving emicizumab in Poland, not including clinical trials. The aim of this paper was to review the most recent data on the role of emicizumab in the management of patients with severe hemophilia A.

Key words: hemophilia A, inhibitor, factor VIII, emicizumab, rFVIIa, aPCC

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Long-term prophylaxis in severe hemophilia A

Severe hemophilia A, defined as a complete deficiency of factor VIII (FVIII) (plasma activity <1 IU/dL) manifests with devastating, inherited bleeding tendency in which repeated, spontaneous and trauma-related hemorrhages into joints, muscles, and various critical organs inevitably lead to disability, reduced health-related quality of life, and premature death. The natural course of the disease however can be modified, or completely averted, by intravenous infusions of deficient clotting factor. Such treatment is referred to as replacement (or substitution) therapy [1].

There are two basic approaches to replacement therapy. One is on-demand therapy consisting in administration of the missing factor at the time of clinically evident bleeding, the other is prophylaxis based on administration of the deficient clotting factor before bleeding occurs with the aim of avoiding bleeding episodes. Prophylaxis can be short-term or long-term, or even lifelong to avoid many, or ideally all, spontaneous and traumatic bleeds [1, 2].

Nowadays, long-term prophylaxis is generally accepted as the best form of treatment for patients with severe hemophilia A. However, FVIII replacement therapy is invasive, expensive, and not widely available. Due to the short half-life of standard FVIII concentrates [standard half-life (SHL)], of about 10 h, no less than three intravenous infusions per week may be required to maintain FVIII levels at >1 IU/dL, which is effective at reducing incidence of breakthrough bleeds [3]. The use of novel recombinant FVIII concentrates with extended half-life (EHL) has slightly increased the interval between treatments but there is still a requirement for lifelong intravenous infusions, which considerably alter patients' quality of life. On top of that, in about 30% of previously untreated patients (PUPs) with severe hemophilia A, treatment with FVIII concentrates is further complicated by the development of FVIII inhibitors, which render FVIII replacement therapies ineffective [4].

Because prophylactic treatment with SHL and EHL FVIII concentrates does not completely eliminate bleeding episodes in patients with severe hemophilia A, is associated

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with the burden of lifelong intravenous injections, and is ineffective in patients with FVIII inhibitors, more effective therapies are urgently needed. One such is emicizumab.

Emicizumab

Emicizumab (Hemlibra®, F. Hoffmann, La Roche, Basel, Switzerland) is a recombinant, humanized, bispecific, asymmetric monoclonal antibody that bridges activated factor IX (FIXa) and factor X (FX) to restore the function of FVIII [5, 6]. In the coagulation process, emicizumab functions like activated FVIII (FVIIIa), although the two molecules show no structural similarity [7]. In fact, the completely different structure of the two molecules has a significant therapeutic benefit: the antibodies that neutralize factor VIII (FVIII inhibitors) are not capable of neutralizing emicizumab. Therefore, emicizumab is able to restore thrombin generation in the plasma of patients with hemophilia A and inhibitors against FVIII.

Unlike clotting factor concentrates for intravenous use, emicizumab can be injected subcutaneously. This is another advantage much appreciated by patients who thus avoid frequent intravenous injections. Moreover, SHL FVIII concentrates for long-term prophylaxis are usually administered every 2–3 days, while emicizumab can be injected every one, two or even every four weeks, depending on the selected dosing schedule [8].

Emicizumab is injected subcutaneously once weekly, at a dose of 3 mg/kg during the first four weeks (loading dose) which results in the steady-state of plasma concentration of the drug. This is the so-called saturation phase. In the 5th week, the mean trough plasma concentration of emicizumab in hemophilia A patients was around 50 µg/mL [8]. This concentration corresponds to c.15% of factor VIII activity; in other words, the hemostatic status of a severe hemophilia A patient on regular emicizumab dosage can be compared to that of a patient with mild hemophilia A with FVIII activity approximately 15% of normal [9]. Detailed descriptions of the pharmacokinetic and pharmacodynamic properties of emicizumab can be found elsewhere [10–12].

Clinical development program for emicizumab

The program of clinical trials to evaluate prophylactic emicizumab involves multi-center, open-label phase III clinical trials, including HAVEN (1 to 4), STASEY, and HOHOEMI [13–18]. Emicizumab was approved in the USA in 2017, and in the EU, Japan and other countries in 2018 on the basis of positive results from the HAVEN 1 trial [13]. The study demonstrated the superiority of emicizumab for long-term bleeding prophylaxis compared to that of by-passing agents (BPAs) administered either prophylactically or on demand. In the HAVEN 1 trial, 63% of patients on emicizumab prophylaxis reported no bleeding episodes which required hemostatic treatment. In HAVEN 2, the percentage of such patients was even higher, at 87%. To date, no such good results have been obtained in evaluation trials of various forms of prophylaxis in severe hemophilia, regardless of the inhibitor status. Table I presents the major outcomes of four HAVEN clinical trials on emicizumab in the management of hemophilia A patients with and without inhibitors against FVIII [13–16].

Recently, Callaghan et al. [19] presented long-term data on the efficacy, safety, and pharmacokinetics of emicizumab used in the HAVEN 1–4 studies. A total of 401 pediatric and adult patients enrolled in the phase III Haven 1–4 studies were followed for a median of 120.4 weeks. The model-based treated annualized bleed rate (ABR) was 1.4 [95% confidence interval (CI): 1.1–1.7]. ABRs declined and then stabilized at <1 in an analysis of 24-week treatment intervals; at weeks 121 to 144 (n =170), the mean treated ABR was 0.7 (95% CI: 0–5.0). During weeks 121 to 144, 82.4% of participants had 0 treated bleeds, 97.6% had ≤3 treated bleeds, and 94.1% reported no treated target joint bleeds [19]. Unsurprisingly, long-term prophylaxis with emicizumab led over time to decreased FVIII consumption in patients without inhibitors, and by-passing agents in those with inhibitors.

Safety profile of emicizumab

The most common adverse events associated with the use of emicizumab are injection site reactions (ISR) [13, 19]; normally they are mild to moderate in intensity. In the HAVEN 1–4 studies, no participants discontinued emicizumab because of ISR [19]. However, the most important adverse events reported in the HAVEN 1 trial were thromembolic events (TE) and thrombotic microangiopathy (TMA) episodes in five patients [13]. All episodes were preceded by the administration of activated prothrombin complex concentrate (aPCC) at a dose of >100 U/kg/day for >24 h. In 4/5 patients, TE and TMA symptoms resolved completely within 1–4 weeks of aPCC discontinuation. One TMA patient died, although the symptoms were reported to have resolved before death. Another TMA patient required several days of intensive therapeutic plasma exchange and renal replacement therapy. In all patients, both aPCC and emicizumab were discontinued. None of the TE and TMA patients received anticoagulant medication. Two of the four patients resumed emicizumab therapy, and no further events were reported.

Based on these results, guidelines have been changed to recommend recombinant factor VIIa (rFVIIa) use and avoid aPCC or, if impossible, use the lowest aPCC doses for the management of bleeding episodes in patients on emicizumab [12, 20–23].

Table I. Data for HAVEN 1–4 trials (based on [13–16])

Study population	No. of bleeds requiring treatment per 12 months* during emicizumab prophylaxis (95% CI)	% of reduced bleeding episodes during emicizumab prophylaxis vs. on demand	% of patients with no treated bleeds reported during study	% of reduced bleeding episodes during emicizumab prophylaxis vs. prior prophylaxis in NIS study
HAVEN 1 Hemophilia A +inhibitor (≥5 UB/mL) Age: ≥12 years Body weight: >40 kg In 24-week period before the trial: ≥6 bleeding episodes (BPAs 'on demand') or ≥2 bleeding episodes (BPA prophylaxis) N =109	2.9 (1.7–5.0)	87	Emicizumab: 63 BPAs ('on demand'): 6	79
HAVEN 2 Hemophilia A +inhibitor (≥5 UB/mL) Age: <12 years Body weight: 3–40 kg In 24-week period before trial: ≥6 bleeding episodes (BPAs 'on demand') or ≥2 bleeding (BPA prophylaxis) N =88	0.2 (0.06–0.62)	Not asssed	Emicizumab: 87 BPAs ('on demand'): not assessed	99
HAVEN 3 Hemophilia A without inhibitors Age: ≥12 years Before trial: n =89 On episodic therapy n =63 and on prophylaxis with FVIII n =152	1.5 (0.9–2.5) (QW) 1.3 (0.8–2.3) (Q2W)	96 (QW) 97 (Q2W)	56 (QW) 60 (Q2W) 0 (no prophylaxis)	68 reduction with emicizumab QW vs. prior FVIII prophylaxis (ABR on emicizumab 1.5 vs. 4.8 on FVIII prophylaxis in NIS)
HAVEN 4 Hemophilia A with and without inhibitors Age: ≥12 years N =48	2.4 (1.4–4.3) (Q4W)	Not assessed	56 (Q4W)	Not applicable (no comparator)

*This value is estimated as follow-up period was <12 months; CI — confidence interval; NIS — a non-intervention study conducted before main clinical trial; BPA(s) — by-passing agent(s); QW — once weekly; Q2W — every two weeks; FVIII — factor VIII; ABR — annualized bleed rate; Q4W — every four weeks

In the study by Callaghan et al. [19], two additional TE episodes not associated with aPCC use were reported; one was device occlusion of a peripherally inserted central catheter (HAVEN 1) and the second was acute myocardial infarction (MI) (HAVEN 3). Both were assessed as unrelated to emicizumab by the investigators, both were resolved, and each individual continued emicizumab. The patient with MI was aged over 65, had previously undiagnosed coronary artery disease, was treated for the event, and recovered [19].

Emicizumab is an immunogenic protein that can stimulate the recipient's immune system to produce the so-called anti-drug antibodies (ADA). As of 2020, in the whole HAVEN trial, 14 out of 398 (3.5%) patients developed ADA, and three (<1%) developed neutralizing anti-drug antibodies to emicizumab [24]. One pediatric hemophilia A patient with

Table II. Laboratory assays to use in presence of emicizumab (acc. to [12, 26], modified)

Assay	Guidance
FVIII activity	Recommended use of chromogenic method with bovine reagents or with human factor IXa and bovine factor X
FVIII inhibitor titer	Recommended to use chromogenic method with bovine factors IXa and X (or with human factor IXa and bovine factor X). Same method should be used for inhibitor titration in blood sample collected prior to inclusion of emicizumab, in order to facilitate interpretation of results in long-term monitoring
ADA	No available commercial test for ADA. If neutralizing ADA suspected, recommended to control emicizumab concentration (*see below*)
	Prolongation to APTT may indicate presence of drug neutralizing antibodies
Emicizumab concentration	Recommended to use a test based on measurement of FVIII activity with one-stage clotting assay with specific emicizumab calibrators to which results are referred

FVIII — factor VIII; ADA — anti-drug antibodies; APTT — activated partial thromboplastin time

inhibitor developed anti-drug antibodies that completely eliminated the pharmacokinetic effect of emicizumab. It was therefore necessary to go back to BPAs [14]. Callaghan et al. [19] have announced a separate paper on long-term immunogenicity of emicizumab, to be published soon.

As of May 2020, 31 fatalities in patients with hemophilia A taking emicizumab had been reported [25]. Median age at death was 58 years; 51% had FVIII inhibitors. The most frequent cause of death was hemorrhage (11/31). No death related to thrombosis or TMA was reported. The authors of this paper concluded that no unique risk of death was associated with emicizumab prophylaxis.

Emicizumab effect on coagulation tests

Emicizumab reduces the activated partial thromboplastin time (APTT) and may therefore be responsible for false APTT-dependent coagulation assay results, FVIII activity included [12, 26]. In severe hemophilia A patients, normalization of the APTT will occur, even at minimum (>5 µg/mL) concentration of emicizumab in plasma. Emicizumab has little effect on prothrombin time (PT) and practically no impact on thrombin time (TT) and fibrinogen concentration in plasma measured with the Clauss method. The effect of emicizumab on PT is minimal, and therefore the results of PT-dependent coagulation tests are considered reliable. Table II sets out selected coagulation assays to use in the presence of emicizumab [12, 26].

Perioperative management of patients with hemophilia receiving emicizumab

Across the HAVEN studies, 215 minor and 18 major surgical procedures were performed [27]. Most of the minor interventions were dental and central venous access device procedures, which went uneventfully without any additional hemostatic therapy in the perioperative period. Nevertheless, in some patients bleeding complications were observed, mostly following dental procedures and in these cases coagulation factor therapy might have been required.

Most major surgeries were successfully managed with prophylactic coagulation factor infusions; in patients without inhibitors, FVIII concentrates were given at usual doses, while in patients with hemophilia A complicated by FVIII inhibitor, rFVIIa was used in all but one patient who underwent laparoscopic appendectomy after a single injection of aPCC at a dose of c.50 U/kg [28, 29]. Suggested management of minor and major surgeries in patients with hemophilia A on emicizumab is set out in Table III.

Real-world experience

Recently, the first results of single-center studies have been published which report physicians' experience with emicizumab in various clinical circumstances [30–32]. Berg et al. [30] evaluated the safety, efficacy, and laboratory monitoring of emicizumab prophylaxis in a cohort of 40 children with severe HA, including 22 non-inhibitor patients and nine babies aged under 12 months. During a median of 45 weeks of follow-up, 20 patients experienced zero bleeds; all breakthrough bleeds were trauma-related. Sixteen surgical interventions were performed in 12 patients, with no thrombotic complications or thrombotic microangiopathy. Prolonged aPTT values normalized after emicizumab initiation, correlating with an increase in emicizumab plasma levels. Emicizumab prophylaxis was safe and well tolerated.

In another observational study, McCary et al. [31] evaluated the efficacy and safety of emicizumab in 93 patients with a median age of 8.6 years, including 49 under 12 years without inhibitors. ABR dropped from 4.4 (inhibitors) and 1.6 (non-inhibitors) to 0.4 (both groups) on emicizumab (p =0.0012 and 0.0025, respectively). There were 28 minor (21 port removals) and two major procedures. Three patients received 1–2 doses of unplanned factor postoperatively to treat minor bleeding events. No patient discontinued therapy, and there were no thrombotic events or deaths.

Table III. Management of minor and major surgical procedures in patients with hemophilia A on emicizumab prophylaxis

Type of surgery	1st-line option	2-nd line option	3-rd line option
Minor surgery in patient without inhibitor	No additional treatment	Tranexamic acid	FVIII concentrates (FVIII plasma activity monitoring) ±tranexamic acid
Major surgery in patient without inhibitor	FVIII concentrates (FVIII plasma activity monitoring) ±tranexamic acid	N/A	N/A
Minor surgery in patient with inhibitor	No additional treatment	Tranexamic acid	FVIII concentrates (FVIII plasma activity monitoring) or rFVIIa ±tranexamic acid* aPCC if FVIII and rFVIIa ineffective**
Major surgery in patient with inhibitor	FVIII concentrates (FVIII plasma activity monitoring) or rFVIIa ±tranexamic acid* aPCC if FVIII and rFVIIa ineffective**	N/A	N/A

*Depending on current inhibitor titer; **activated prothrombin complex concentrate (aPCC) should be given in low doses i.e. <50 U/kg/dose and <100 U/kg/24 h; FVIII — factor VIII; N/A — not applicable; rFVIIa — recombinant factor VIIa

Lewandowska et al. [32] reported on 20 minor and five major surgeries performed in 17 and five patients on emicizumab prophylaxis respectively. Overall, 9/20 minor surgeries were planned to occur with emicizumab as the sole hemostatic agent; of these, four required additional coagulation factor. Three of the 11 minor surgeries with planned additional coagulation factor resulted in non-major bleeds; all were safely managed with additional coagulation factor. All five major surgeries were planned with additional hemostatic agents; there was one bleed, likely triggered by physical/occupational therapy in a patient after elbow surgery. Four patients with hemophilia A complicated by inhibitors underwent three minor and one major surgeries. Three of them received additional therapy with rFVIIa; no thrombotic complications occurred. However, two patients developed minor bleeding complications following dental extraction and port removal respectively. Overall, there were no major bleeds, thrombotic events or deaths.

Emicizumab in Poland

Emicizumab prophylaxis was launched in Poland in 2020 in a group of 30 severe hemophilia A patients with high titer inhibitor against factor VIII. As of April 2021, a total of 42 pediatric and adult patients with hemophilia A complicated by FVIII inhibitor were receiving emicizumab in Poland (not including clinical trials). Eligibility criteria for long-term bleeding prophylaxis with emicizumab are set out in the National Program for 2019–2023. For Polish hemophilia A patients with no inhibitor, Hemlibra® is not as yet available. Results of the interim analysis of the efficacy and safety of emicizumab in adult Polish patients with hemophilia A complicated by FVIII inhibitor will be presented at the Polish Society of Haematology and Transfusion Medicine, (PTHiT, *Polskie Towarzystwo Hematologów i Transfuzjologów*) Congress 2021. It is worth noting that in 2020, the Group for Hemostasis of the Polish Society of Hematology and Transfusion Medicine published guidelines on emicizumab use in hemophilia A patients with inhibitors against factor VIII [12].

Author's contributions

JW — sole author.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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