Bridging the Missing Link with Emicizumab: A Bispecific Antibody for Treatment of Hemophilia A

Georg Gelbenegger1 Christian Schoergenhofer1 Paul Knoebl2 Bernd Jilma1

1 Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria
2 Division of Hematology, Department of Internal Medicine I, Medical University of Vienna, Vienna, Austria

Address for correspondence Bernd Jilma, MD, Department of Clinical Pharmacology, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria (e-mail: Bernd.Jilma@meduniwien.ac.at).

Introduction

Deficiency of coagulation factor VIII (FVIII), commonly known as hemophilia A, is a severe bleeding disorder,1 representing 80 to 85% of the total hemophilia population.2 Hemophilia A is an X-linked recessive bleeding disorder, thereby primarily affecting males.3 Hemophilia A is classified based on the residual FVIII activity level and is defined as severe (coagulation factor activity level <1%), moderate (1–5%), or mild (6–40%).4 The residual FVIII level depends on the type of mutation in the FVIII gene. Classification of hemophilia also correlates well with clinical profiles and bleeding symptoms.4,5 Approximately two-thirds of patients with hemophilia A suffer from severe FVIII deficiency.6 Predominantly in patients with severe hemophilia A, total deficiency of FVIII can lead to serious joint bleedings, muscle bleedings, soft tissue bleedings, and life-threatening bleeding manifestations such as intracranial hemorrhages,7,8 which can occur spontaneously.6 Hemophilic arthropathy is a serious complication of hemophilia-induced joint bleedings,9 caused by synovial inflammation with subsequent release of inflammatory cytokines and matrix-metalloproteases leading to progressive degradation of the cartilage.10

Abstract

Hemophilia A, characterized by absent or ineffective coagulation factor VIII (FVIII), is a serious bleeding disorder that entails severe and potentially life-threatening bleeding events. Current standard therapy still involves replacement of FVIII, but is often complicated by the occurrence of neutralizing alloantibodies (inhibitors). Management of patients with inhibitors is challenging and necessitates immune tolerance induction for inhibitor eradication and the use of bypassing agents (activated prothrombin complex concentrates or recombinant activated factor VII), which are expensive and not always effective. Emicizumab is the first humanized bispecific monoclonal therapeutic antibody designed to replace the hemostatic function of activated FVIII by bridging activated factor IX and factor X (FX) to activate FX and allow the coagulation cascade to continue. In the majority of hemophilic patients with and without inhibitors, emicizumab reduced the annualized bleeding rate to almost zero in several clinical trials and demonstrated a good safety profile. However, the concurrent use of emicizumab and activated prothrombin complex concentrate imposes a high risk of thrombotic microangiopathy and thromboembolic events on patients and should be avoided. Yet, the management of breakthrough bleeds and surgery remains challenging with only limited evidence-based recommendations being available. This review summarizes published clinical trials and preliminary reports of emicizumab and discusses the clinical implications of emicizumab in treatment of hemophilia A.

Keywords
► hemophilia
► emicizumab
► bleeding
► bispecific antibody
► coagulation

Keywords
► hemophilia
► emicizumab
► bleeding
► bispecific antibody
► coagulation

received February 23, 2020
accepted after revision June 8, 2020

DOI https://doi.org/10.1055/s-0040-1714279.
ISSN 0340-6245.

© 2020 Georg Thieme Verlag KG
Stuttgart · New York

License terms
Role of Factor VIII in the Coagulation Cascade

It is well recognized that the intrinsic pathway is not an accurate model of hemostasis in vivo. Activation of the coagulation cascade is mostly triggered by the tissue factor (TF) pathway, which involves complex formation of TF and activated factor VII (FVIIa) at the site of injury (Fig. 1A). The TF/FVIIa complex not only activates factor X (FX) directly, but also activates factor XI (FIX) which further sustains activated FX (FXa), leading to generation of thrombin. Thrombin itself may also activate FXI and FVIII, thereby creating a positive feedback loop. FXa when associated with phospholipids or the TF/FVIIa complex is also a potent activator of FVIII. Although not causally involved in the activation process of coagulation, FVIII helps to further maintain and strengthen the production of FXa, ultimately resulting in the generation of thrombin and formation of a stable fibrin clot. In patients with hemophilia A, lack or dysfunction of FVIII impedes physiologic coagulation function and increases the risk of bleeding.

Factor Replacement Therapy

FVIII replacement with FVIII concentrates is still the treatment of choice in patients suffering from moderate and, in particular, severe hemophilia. FVIII concentrates can either be plasma-derived (originating from human donor blood) or recombinant (biotechnologically produced from genetically modified cells). Several modified recombinant FVIII products with extended half-lives have been released to increase dosing intervals and obtain higher trough levels. Treatment can either be prophylactic or episodic. Prophylactic FVIII replacement has been shown to significantly reduce bleeding events and slow down joint deterioration. While prophylactic treatment is the more effective way to prevent bleeding and long-term complications, it is expensive, burdensome, and may rarely necessitate central venous access which is associated with infection and thrombosis. Alternatively, episodic FVIII replacement therapy may be suitable for patients with mild or moderate factor deficiency and a milder bleeding phenotype. The decision which patient population is eligible for and should receive episodic or prophylactic replacement therapy depends on individual patient-related factors (rate and severity of bleeding, venous access, personal preference, etc.).

Yet, there are considerable downsides to FVIII replacement. First, it is expensive and not available everywhere. So far, FVIII can only be given intravenously, implicating that repeated venipunctures are required for a regular, long-term treatment. This often coincides with a reduced patient compliance followed by a worse outcome. The use of FVIII replacement therapy is further complicated by a high interindividual variability in FVIII pharmacokinetics (PK), which necessitates tailored treatment regimens for individuals leading to frequent dose corrections to maintain sufficient FVIII trough levels. In the past, FVIII replacement using plasma-derived concentrates has led to the transmission of blood-borne diseases including hepatitis B and C, and human immunodeficiency virus, which has caused significant morbidity and mortality. Since then, improvement in processing of FVIII concentrates has led to a significant decrease of viral infections; however, pathogen transmission through plasma-derived FVIII concentrate infusion yet remains a potential risk.

Inhibitors

Probably the most challenging aspect of factor replacement therapy in patients with hemophilia A is the occurrence of inhibitory alloantibodies against FVIII. Such inhibitors can rise to very high titers (high responders) and neutralize circulating FVIII rendering replacement therapy ineffective. In patients with severe hemophilia A, anti-FVIII antibodies form in 25 to 40% within the first 50 exposure days. Inhibitors are associated with increased mortality, limitations of physical function, orthopedic complications, and decreased quality of life and increased health care costs when compared with patients without inhibitors. Inhibitors necessitate alternative treatment approaches such as
immune tolerance induction (ITI) or the use of bypassing agents (BPAs), recombinant FVIIa (rFVIIa, NovoSeven), and activated prothrombin complex concentrate (APCC, FEIBA). However, the use of BPAs is not as effective as replacement of FVIII, and has several other disadvantages (very high costs, short half-life, and risk of thromboembolic events). Despite its mechanism of inhibitor elimination still being unclear, ITI shows a response rate of 50 to 75%, yet, it requires long-term infusion of high doses of FVIII concentrates and can take years to show effect. Treatment of hemophilia A complicated by FVIII inhibitors requires a high amount of human and economic resources.

In recent years, multiple novel FVIII products have been made available, mostly improving PK aspects, but showing varying results with respect to immunogenicity. However, development of FVIII inhibitors substantially limits the use of factor replacement therapy. Therefore, the unmet medical need for a treatment approach for hemophilia that is easy to use, with a long-lasting effect regardless of the presence of FVIII inhibitors, has led to the development of emicizumab, a new bispecific therapeutic antibody mimicking the effect of FVIII.

This review focuses on the safety and efficacy of emicizumab and discusses its clinical implications and potential extended use.

Emicizumab

Emicizumab (Hemlibra, Roche, Switzerland) is the first commercially available nonfactor replacement product for treatment of congenital hemophilia A. In the United States, it was first approved by the Food and Drug Administration (FDA) in 2017 for the use in patients with congenital hemophilia A with inhibitors, with its indication subsequently being extended for prophylactic use in hemophilic patients with and without inhibitors in 2018. In the European Union, emicizumab is approved for the routine prophylaxis of bleeding episodes in patients with congenital hemophilia A with FVIII inhibitors or severe hemophilia A without inhibitors.

Emicizumab is injected subcutaneously with FDA-approved maintenance dose regimens of 1.5 mg/kg once every week (QW), 3 mg/kg once every 2 weeks (Q2W), or 6 mg/kg once every 4 weeks (Q4W). The recommended loading dose for all treatment regimens is 3 mg/kg QW for the first 4 weeks.

So far, results from four large HAVEN trials have been published (Tables 1 and 2).

Mechanism of Action and Pharmacodynamic Profile

Emicizumab is a humanized bispecific monoclonal antibody (IgG4) that binds to both the activated FIX (FIXa) and FX. It is therefore designed to mimic the function of missing or deficient FVIII, which is an essential part of effective hemostasis. Emicizumab aligns FIXa and FX in a suitable spatial position, thereby promoting the interaction between the two coagulation factors and accelerating FX activation by FIXa (Fig. 1B). However, there are considerable differences between the natural FVIII and emicizumab. As expected for an antibody, emicizumab binds only to a single site within the FIX and FX molecules, whereas FVIII has multiple interaction sites. Therefore, emicizumab shows substantially less affinity for its substrates, it cannot differentiate between zymogen and enzyme (FIX and FX vs. FIXa and FXa), and it lacks natural regulation of its activity, i.e., the activation by thrombin and the inactivation by protein C.

Due to its structural difference to FVIII, emicizumab does not induce the development of FVIII inhibitors.

The pharmacodynamic (PD) response to emicizumab correlates with plasma concentrations of emicizumab. In ex vivo FVIII-neutralized plasma from healthy subjects who received emicizumab in different doses, emicizumab dose-dependently shortened the activated partial thromboplastin time (aPTT). Similarly, peak thrombin generation increased in a dose-dependent manner. In healthy volunteers without FVIII neutralization, emicizumab only slightly shortened the aPTT but did not increase peak thrombin generation. This minimal effect of emicizumab in healthy volunteers can be explained by the higher affinity of FVIIIa than that of emicizumab for FXa.

In patients with hemophilia A, emicizumab dose-dependently shortened the aPTT and increased peak thrombin generation. Initiation of emicizumab (6 mg/kg) in hemophilic patients normalized the aPTT within 8 hours and increased peak thrombin generation over the following weeks.

Pharmacokinetic Profile and Immunogenicity

Following subcutaneous injection of 1 mg/kg, emicizumab showed an absolute bioavailability of 80 to 93% and a mean absorption half-life of 1.7 days. The mean elimination half-life of emicizumab is 1 month ranging from 28.8 to 34.4 days (Table 3). The long half-life of emicizumab is assumed to be due to its IgG4 structure including an altered amino acid sequence that lowers its isoelectric point and reduces its elimination. The mean apparent volume of distribution of emicizumab is 11.4 L. Plasma concentrations of emicizumab increased in a dose-dependent manner.

Emicizumab showed a first-order elimination phase. Mean trough plasma concentrations depend on the applied dose regimen (after a loading dose of 3 mg/kg QW for 4 weeks): when emicizumab was given QW at a dose of 1.5 mg/kg, mean trough plasma levels were above 50 µl/mL. Dosing regimens injecting emicizumab Q2W (3 mg/kg) and Q4W (6 mg/kg) resulted in mean trough plasma levels of 45 to 50 and 38 to 40 µg/mL respectively (Table 3). The PK of emicizumab are unaffected by age (1–77 years), race, inhibitor status, mild or moderate hepatic impairment, and mild or moderate renal impairment.

Further, the immunogenic potential of emicizumab remains to be better defined. Six studies provide data on the occurrence of antidrug antibodies in healthy subjects or patients undergoing treatment with emicizumab (Table 3). In the first-in-man trial, one subject tested positive for anti-emicizumab antibodies even at baseline (before drug administration) and another developed de novo antibodies causing a shortening
Table 1 Key demographics of included trials

| Key demographics                  | HAVEN 1                      | HAVEN 2                      | HAVEN 3                      | HAVEN 4                      | First-in-man trial | First-in-patient trial | HOHOEMI | STASEY                                                                 |
|----------------------------------|------------------------------|------------------------------|------------------------------|------------------------------|--------------------|------------------------|----------|------------------------------------------------------------------------|
| Authors (publication year)       | Oldenburg et al (2017)       | Young et al (2019)           | Mahlangu et al (2018)        | Pipe et al (2019)            | Uchida et al (2016) | Shima et al (2016)     | Shima et al (2019)     | Data cut-off: October 15, 2018                                      |
| Population                       | Adult/adolescent (≥12 y) PwHA with inhibitors | Pediatric (<12 y) PwHA with inhibitors | Adult/adolescent (≥12 y) PwHA without inhibitors | Adult/adolescent (≥12 y) PwHA with or without inhibitors | Healthy Japanese and white male subjects (20–44 y) | Adult/adolescent (12–59 y) PwHA with or without inhibitors | Pediatric (<12 y, >3 kg) PwHA without inhibitors | Adult/adolescent (≥12 y) PwHA with inhibitors                              |
| Treatment duration               | 24 wk                        | 52 wk                        | 24 wk                        | 24 wk                        | Single-dose, follow-up ranging from 4 to 24 wk | 12 wk                 | 24 wk                 | 24 wk                                                                 |
| Dosing                           | 1.5 mg/kg QW                 | 1.5 mg/kg QW, 3 mg/kg Q2W, 6 mg/kg Q4W | 1.5 mg/kg QW, 3 mg/kg Q2W    | 6 mg/kg Q4W                  | 0.001 mg/kg, 0.01 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg | 0.3 mg/kg QW, 1 mg/kg QW, 3 mg/kg QW | 3 mg/kg Q2W, 6 mg/kg Q4W  | 1.5 mg/kg QW                                                            |
| Median duration of exposure [wk] (IQR) | 107.4 (84.2–127.1)           | 75.1 (46.2–80.4)             | 84.4 (79.1–92.6)             | 68.1 (66.2–68.1)             | n/a                | n/a                   | Q2W 39.1 (36.4–40.3), Q4W 32.1 (24.1–36.4) | 39.2 (4.4–57.1)                                                       |

Abbreviations: IQR, interquartile range; kg, kilogram; mg, milligram; PwHA, persons with hemophilia A; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks.
**Table 2** Overview of study design, sample size, and inclusion and exclusion criteria of included trials

| Methods          | HAVEN 1                                   | HAVEN 2                                   | HAVEN 3                                   | HAVEN 4                                   | First-in-man trial     | First-in-patient trial | HOHOEMI                  | STASEY                   |
|------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------|------------------------|-------------------------|-------------------------|-------------------------|
| **Design**       | Phase III, open-label, multicenter, randomized | Phase III, multicenter, open-label       | Phase III, open-label, multicenter, randomized | Phase III, single-arm, multicenter, open-label | Phase I, first-in-human, single-center, double-blind, randomized, placebo-controlled, interindividual dose-escalation | Open-label, nonrandomized, interindividual dose-escalation | Multicenter, open-label, nonrandomized | Phase IIb, single-arm, open-label, multicenter |
| **N**            | 113                                       | 88                                        | 152                                       | 48                                        | 64                     | 18                      | 13                      | 88                      |
| **Inclusion criteria** | 12 years of age or older, congenital hemophilia A, high titer of FVIII inhibitors, receiving episodic or prophylactic treatment with bypassing agents | Children with congenital hemophilia A with FVIII inhibitors, receiving episodic or prophylactic treatment with bypassing agents | 12 years of age and older, severe congenital hemophilia A (<1% of normal FVIII activity in blood) or hemophilia A with FVIII inhibitors, undergoing treatments with either FVIII concentrates or bypassing agents | Healthy subject, age between 20 and 44 years, BMI 18.5 to <25.0 (Japanese subjects), BMI 18.5 to <30.0 (white subjects) | Severe congenital hemophilia A, with/without FVIII inhibitors, age 12–59 years, chronic prophylaxis with FVIII in patients without inhibitors, episodic or prophylactic treatment with bypassing agents in patients with inhibitors, six or more bleeding episodes in the last 6 months | <12 years old, weighing over 3 kg, severe congenital hemophilia A without FVIII inhibitors, age 12–59 years, chronic prophylaxis with FVIII in patients without inhibitors, episodic or prophylactic treatment with bypassing agents in patients with inhibitors, six or more bleeding episodes in the last 6 months | 12 years of age or older, diagnosis of hemophilia A with persistent inhibitors against FVIII, treatment with bypassing agents or FVIII concentrates over the last 6 months (episodic or prophylactic), adequate hematologic, hepatic, or renal function |
| **Exclusion criteria** | Inherited or acquired bleeding disorder other than hemophilia A, ongoing ITI or treatment with FVIII, treatment within the last 12 months for, or current signs of, thromboembolic disease | Inherited or acquired bleeding disorder other than hemophilia A, ongoing ITI or prophylaxis treatment with FVIII, other disease that may increase the risk of bleeding or thrombosis | Inherited or acquired bleeding disorder other than hemophilia A, treatment within the past 12 months for, or current signs of, thromboembolic disease | Inherited or acquired bleeding disorder other than hemophilia A, ongoing or planned ITI therapy, participants at high risk for TMA, previous (within the last 12 months) or current treatment for thromboembolic disease or signs of thromboembolic disease | Current history of a bleeding disorder other than congenital hemophilia A, clinically significant infection (hepatitis B or C virus), value for protein C activity, free protein S antigen level, reduced antithrombin activity | Inherited or acquired bleeding disorder other than congenital hemophilia A, thromboembolic diseases within the past 12 months and high risk for TMA (based on previous or familial history of TMA (e.g., thrombotic thrombocytopenic purpura, atypical hemolytic uremic syndrome) | Inherited or acquired bleeding disorder other than hemophilia A, ongoing (or plan to receive during the study) ITI therapy, High risk for TMA (previous in the last 12 months) or current treatment for thromboembolic disease (with the exception of catheter-associated thrombosis) or current signs of thromboembolic disease |

Abbreviations: FVIII, factor VIII; ITI, immune tolerance induction; TMA, thrombotic microangiopathy.
of emicizumab half-life. The first study of emicizumab in hemophilic patients found antidrug antibodies in one patient at baseline, but without neutralizing ability. In the HAVEN 1 trial, no subject tested positive for antidrug antibodies; however, two patients showed PK profiles indicative of such. The HAVEN 2 trial identified four patients with antidrug antibodies, two of which had neutralizing ability. In HAVEN 3, no de novo antidrug antibodies were identified; however, measurement discrepancies occurred in two patients and one patient intermittently tested positive after ITI. No antidrug antibodies were found in patients in HAVEN 4. Due to the limited sample size of studies available, it is difficult to accurately derive the incidence of antidrug antibodies and the proportion of antibodies with neutralizing potential. Further studies with long-term follow-up periods are needed to better characterize immunogenicity.

### Efficacy

#### Overall Analysis

Pooled data from HAVEN 1–4 revealed the annualized bleeding rate (ABR) under treatment with emicizumab to be 1.5 (95% confidence interval [CI]: 1.20–1.84) over a median duration of exposure of 83 weeks. Three different treatment regimens have been tested in the HAVEN trials: subcutaneous injection of emicizumab of 1.5–mg/kg QW, 3 mg/kg Q2W, or 6 mg/kg Q4W. All treatment regimens were preceded by four loading doses of 3 mg/kg QW. Emicizumab QW, Q2W, and Q4W regimens were associated with a mean ABR across HAVEN 1–4 of 1.6, 0.8, and 2.3, respectively. ABRs of the four individual HAVEN trials are shown in Table 4. In every treatment cohort of the HAVEN trials, at least 50% of patients (range 56–90%) had zero treated bleeding events. The proportion of patients with no bleeding events increased over time in all four trials. Across HAVEN 1–4, emicizumab was associated with an ABR for spontaneous bleeds of 0.6 (95% CI: 0.5–0.8) and for joint bleeds of 1.0 (95% CI: 0.8–1.3). Again, the proportion of patients with zero bleeding events (spontaneous and joint) increased over time. Further, emicizumab was associated with a resolution of 99% of target joints (target joints were defined as major joints [e.g., hip, elbow, wrist, shoulder, knee, and ankle] in which ≥3 bleeding events occurred over a 24-week period; target joint resolution was defined as ≤2 bleeding events in a 52-week period in a joint previously defined as a target joint) in patients across HAVEN 1–4.

In the Japanese pediatric HOHOEMI trial, although small in sample size, Q2W and Q4W treatment regimens showed ABRs for treated bleeding events of 1.3 and 0.7, respectively. Similar to previous studies, interim results from the STASEY trial report an ABR of 0.5 for treated bleeding events.

#### Comparison of Efficacy in Patients with versus without FVIII Inhibitors

Three studies, HAVEN 1, 2, and STASEY, evaluated the efficacy of emicizumab in hemophilic patients with FVIII inhibitors only. Emicizumab resulted in ABRs of treated bleeds of 2.9, 0.3, and 0.5 (all QW), respectively.
Table 4  Efficacy outcomes of included trials

| Efficacy | HAVEN 1 | HAVEN 2 | HAVEN 3 | HAVEN 4 | First-in-man trial | First-in-patient trial | HOHOEMI | STASEY |
|----------|---------|---------|---------|---------|-------------------|-----------------------|---------|--------|
| Dosing regimen(s) | QW | QW, Q2W, Q4W | QW, Q2W | Q4W | n/a | 0.3 mg, 1 mg, 3 mg QW | Q2W, Q4W | QW |
| ABR of treated bleeding events (95% CI) (% reduction vs. reference arm) | 2.9 (1.7–5.0) (87% reduction) | 0.3 (0.17–0.50), 0.2 (0.03–1.72), 2.2 (0.69–6.81) | 1.5 (0.9–2.5) (96% reduction), 1.3 (0.8–2.3) (97% reduction) | 2.4 (1.4–4.3) n/a | n/a | 1.3 (0.6–2.9), 0.7 (0.0–3.1) | 0.5 (0.29–1.00) |
| % Zero bleeding events | 63 | 76.9, 90.0, 60.0 | 55.6, 60.0 | 56.1 | n/a | 73 (with inhibitors), 71 (without inhibitors) | 33.3, 71.4 | 80.7 |
| All bleeding events | 5.5 (3.6–8.6) | 3.2 (1.94–5.22), 1.5 (0.62–3.40), 3.8 (1.42–10.11) | 2.5 (1.6–3.9), 2.6 (1.6–4.3) | 4.5 (3.1–6.6) n/a | 4.4 (0.0–59.5), 0.0 (0.0–4.3), 0.0 (0.0–4.2) | 14.1 (7.6–26.2), 21.8 (9.2–51.8) | 1.4 (0.91–2.24) |
| Treated spontaneous bleeding (ABR) | 1.3 (0.7–2.2) vs. 16.8 (9.9–28.3) | 0.0 (0.01–0.10), not estimable 0.8 (0.05–12.00) | 1.0 (0.5–1.9), 0.3 (0.1–0.8) | 0.6 (0.3–1.5) n/a | n/a | 0.2 (0.0–1.6), n/a | 0.2 (0.08–0.34) |
| Treated joint bleeding (ABR) | 0.8 (0.3–2.2) vs. 6.7 (2.0–22.4) | 0.2 (0.08–0.29), 0.2 (0.03–1.72), 1.7 (0.60–4.89) | 1.1 (0.6–1.9), 0.9 (0.4–1.7) | 1.7 (0.8–3.7) n/a | n/a | 0.9 (0.3–2.3), n/a | 0.3 (0.10–0.84) |
| Treated target-joint bleeding (ABR) | 0.1 (0.0–0.6) vs. 3.0 (1.0–9.1) | Not estimable 0.2 (0.03–1.72), 0.5 (0.05–5.88) | 0.6 (0.3–1.4), 0.7 (0.3–1.6) | 1.0 (0.3–3.3) n/a | n/a | n/a, n/a | 0.1 (0.03–0.18) |
| Proportion of resolved target joints (%) | 98.7 | 100 | 99.2 | 100 | n/a | n/a | n/a, n/a | n/a |

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks.
Two studies, HAVEN 3 and HOHOEMI, only included patients without FVIII inhibitors.\textsuperscript{55,60} Emicizumab was associated with ABRs of treated bleeds of 1.5 (QW) and 1.3 (Q2W), respectively. HAVEN 4 included both patients with and without inhibitors; however, 88% of patients in the expansion cohort had no FVIII inhibitors. The ABR for treated bleeds in HAVEN 4 was 2.4 (Q4W).

**Comparison of Efficacy According to Different Treatment Regimens (QW versus Q2W versus Q4W)**

Six studies evaluated three treatment regimens. The median ABR of treated bleeds of the QW, Q2W, and Q4W treatment regimens, pooled from all studies, was 1, 1.3, and 2.2, respectively.

**Safety and Drug Interactions**

Injection-site reactions were the most common treatment-related adverse events and frequently reported across all HAVEN trials (\( n = 104; 26.1\% \)).\textsuperscript{59} All injection-site reactions were of mild or moderate severity, most of which (93%) resolved without treatment. Other adverse events included headache (15%), arthralgia (15%), pyrexia (6%), and diarrhea (6%).\textsuperscript{58} A total of 103 serious adverse events were reported in 71 participants with hemorrhage and hemorrhathisis being reported by \( \geq 5 \) participants.

Adverse events of special interest occurred in five patients of the HAVEN 1 trial. Of these, three patients developed thrombocytopenia (TMA), one patient suffered from cavernous sinus thrombosis, and another patient suffered from skin necrosis/superficial thrombophlebitis. One patient with TMA developed rectal bleeding, refused treatment with blood transfusions, and subsequently died. His death was considered unrelated to emicizumab due to the resolving TMA at the time.

Notably, the occurrence of all five coagulation-associated adverse events was associated with the concomitant use of APCC at doses of \( > 100 \) U/kg/d for a time period of more than 1 day. None of the patients receiving concomitant treatment with emicizumab and APCC of any dose for only 1 day had any thromboembolic events. Otherwise, in a retrospective analysis of real-world patients, one patient developed postoperative thrombosis/TMA in association with APCC despite emicizumab discontinuation 1 month prior to the surgery.\textsuperscript{62} The pathomechanism of TMA caused by concomitant use of emicizumab and APCC is probably the crosslinking of the activated factors contained in the APCC.\textsuperscript{54} Interestingly, the incidence of TMA was limited to APCC only; no cases of TMA or thromboembolic events have been linked to the concomitant use of rFVIIa. Moreover, management of bleeding episodes with FVIII in emicizumab-treated patients without inhibitors was also not associated with the occurrence of TMA or thromboembolic events.

One patient in the HAVEN 2 trial was believed to suffer from a systemic hypersensitivity reaction due to symptoms of abdominal pain and cough but upon later medical review his symptoms were confirmed not to be linked to anaphylaxis.

In the HOHOEMI trial, two patients experienced serious adverse events unrelated to the study drug. No thromboembolic events, TMA, or systemic hypersensitivity reactions were observed.\textsuperscript{60}

In the STASEY trial, of 17 patients who experienced a treated bleeding event, 16 were concomitantly treated with rFVIIa and one was treated with standard FVIII. There was no occurrence of any thromboembolic event or TMA.\textsuperscript{61}

**Surgery**

In total, 31.6% (126/399) of patients in HAVEN 1–4 underwent at least one surgical procedure.\textsuperscript{63} Of 233 surgeries performed, 18 were deemed major surgeries and 215 were deemed minor surgeries. One hundred forty-one of the minor surgeries were managed without prophylactic infusion of coagulation factor and over 90% of patients had no treated postoperative bleeding events. Of the 18 major surgeries, all three that were managed without prophylactic administration of coagulation factor had no treated postoperative bleeds. Of the remaining 15 patients treated with prophylactic coagulation factor, only one had a treated bleeding event. Major surgeries included five cases of arthroplasty with only one occurrence of bleeding due to surgery.

Further, the successful use of emicizumab with perioperative administrations of rFVIIa in a major surgery has been described in patients receiving total hip arthroplasty.\textsuperscript{64,65} Another patient with acquired hemophilia A under treatment with emicizumab underwent percutaneous coronary intervention and received periprocedural loading with 325 mg aspirin and 600 mg clopidogrel. He was successfully treated and continued dual-antiplatelet therapy without breakthrough bleeding events or need for BPA administration.\textsuperscript{66}

**Health-Related Quality of Life**

Health-related quality of life (HR-QoL) was assessed using the Haem-A-Qol physical health subscale score at week 25. Generally, improvement of HR-QoL was seen across all published HAVEN trials. Further, emicizumab was associated with fewer missed days at school or work\textsuperscript{53,67} and a reduced number of days hospitalized.\textsuperscript{67} Almost all patients preferred emicizumab treatment over prophylaxis with FVIII or BPAs.\textsuperscript{53,55}

**Laboratory Testing**

Assessment of the hemostatic function and FVIII activity in patients under treatment with emicizumab needs special attention.\textsuperscript{66,69} Since emicizumab causes a significant shortening of the aPTT even at very low concentrations,\textsuperscript{52,69} use of conventional aPTT tests is futile. Diluted aPTT, however, correlates well with the plasma emicizumab concentration.\textsuperscript{70}

Conventional FVIII activity assays were found to be either oversensitive or insensitive to emicizumab, which precludes their use. However, a modified FVIII one-stage assay calibrated against emicizumab accurately quantifies FVIII activity and measures emicizumab concentrations.\textsuperscript{71}
To differentiate between the PD effect of emicizumab and the endogenous residual FVIII activity, chromogenic FVIII assays using two different reagents need to be used.\textsuperscript{72} While the chromogenic assay using bovine reagents can detect the endogenous FVIII activity, the one using human reagents assesses emicizumab’s effect.\textsuperscript{59}

For measurement of inhibitors under concurrent treatment with emicizumab, a chromogenic Bethesda assay using bovine reagents can be used.\textsuperscript{73}

Although not routinely done, rotational thromboelastometry (ROTEM; Pentapharm GmbH, Munich, Germany) may be used for assessment of coagulation function in emicizumab-treated patients. In particular, clotting time and clot formation time of the nonactivated thromboelastometry test (native coagulation, NATEM) showed a dose-dependent response to emicizumab.\textsuperscript{74} Thromboelastometry has also been used to assess coagulation function in an in vitro experiment involving emicizumab, APCC, and rFVIIa.\textsuperscript{75} Clot waveform analysis may also be a promising tool for coagulation assessment.\textsuperscript{76} The thrombin generation assay has been shown to be a useful marker of hemostatic function in patients under treatment with emicizumab\textsuperscript{77} and is also helpful in the assessment of coagulation in emicizumab-treated patients receiving concomitant treatment with BPAs.\textsuperscript{78}

**Discussion**

So far, three large trials (HAVEN 1, 3, and 4), evaluating the safety, efficacy, and PK of emicizumab in adults and adolescents with hemophilia A, have been published.\textsuperscript{53,55,56} All three of them showed emicizumab to significantly reduce ABRs. Additionally, results from the HAVEN 2 trial, including only children <12 years (2–11 years), have been published, further substantiating the findings of previous studies.\textsuperscript{57} The recently published HOHOEMI trial and interim results from the STASEY trial also confirmed emicizumab’s efficacy.\textsuperscript{60,61}

While showing a significant decrease in bleeding events, the HAVEN trials lack prospective data comparing emicizumab versus standard prophylaxis with either FVIII or BPAs. Instead, direct comparison of emicizumab with standard care is performed through a noninterventional study, comparing intra-individual patient data. Of note, HAVEN 4 features only a single experimental arm (Q4W).

Intravenous comparison of HAVEN 3, including hemophilic patients without inhibitors, who previously received prophylaxis with FVIII, showed emicizumab prophylaxis to be associated with a 68% lower ABR.\textsuperscript{84}

Noninterventional study results from HAVEN 1 and 2, including hemophilic patients with inhibitors under previous prophylactic treatment with BPAs, showed a 79 and 99% decreased ABR, respectively, with emicizumab prophylaxis, indicating a larger effect size of emicizumab prophylaxis in inhibitor patients.

**Bleeding under Treatment with Emicizumab**

Regardless of the impressive clinical performance of emicizumab, breakthrough bleeding events may still occur and call for additional episodic treatment with either FVIII or BPAs, depending on the presence of inhibitors. Management of breakthrough bleeding proves especially challenging in patients with inhibitors as outlined by the HAVEN 1 trial.

While the concurrent use of APCC and emicizumab imposes a high prothrombotic risk, the concomitant use of rFVIIa in the context of breakthrough bleeding events under emicizumab prophylaxis has so far not been associated with TMA or thromboembolic events\textsuperscript{79} and is recommended as first-line treatment in a recent guidance paper by the United Kingdom Haemophilia Centre Doctors’ Organisation (UKHCDO).\textsuperscript{80} If, after administration of rFVIIa, the bleeding event does not resolve, treatment with FVIII should be initiated. Usage of APCC should only be considered unless no other option is available.\textsuperscript{80}

Another review from the French network on inherited bleeding disorders (MHÉMÉO), the French Reference Centre on Haemophilia, in collaboration with the French Working Group on Perioperative Haemostasis (GIHP) also favors rFVIIa as first-line treatment in a bleeding patient with inhibitors treated with emicizumab, with a similar downstream treatment algorithm. Optionally, tranexamic acid can be given as a supportive measure to rFVIIa.\textsuperscript{81}

Further, the Italian Association of Haemophilia Centres (AICE) have provided a practical guidance paper on how to manage patients with hemophilia A and inhibitors under treatment with emicizumab in the emergency department.\textsuperscript{82}

However, the uncritical, permissive use of rFVIIa in emicizumab-treated patients is unwarranted, since the results of the bleeding analysis from HAVEN 1, 2, and 4 show some major limitations.\textsuperscript{79} First, universal application of the study is precluded by the exclusion of patients with a high thrombotic risk from the included trials. Second, around half of the patients were exposed to only a single-dose treatment of rFVIIa, leaving information on repeated use unknown. Lastly, the study lacks information on patients in the clinical setting of infection (sepsis), trauma, and major surgery.\textsuperscript{83} In hemophiliacs without inhibitors, however, breakthrough bleeding can easily be treated with FVIII concentrates, which should be administered as soon as possible. For joint bleeds and soft tissue bleeds, a dose of approximately 25 units/kg is recommended.\textsuperscript{84}

**Emicizumab versus Standard-of-Care Treatment**

Emicizumab’s exact place in future guidelines remains to be further discussed, yet, convincing arguments can be made for its primary use.

First, patients with poor venous access are spared repeated venipuncture attempts or even the installation of an intravenous catheter, which involves the risk of thrombosis and infection.

Second, in previously untreated patients (PUPs), the initiation of emicizumab could enable (almost) complete discontinuation of FVIII replacement, which includes the prevention of inhibitor development in the first place. In that case, FVIII concentrates would exceptionally be used to treat breakthrough bleeding events, which might potentially slow down or even preclude the development of inhibitors. Inhibitor development is not only dependent on the timing of FVIII
infusion but also on the frequency and intensity of treatment (e.g., during bleeding episodes). During HAVEN 3, emicizumab reduced the ABR to zero in more than 50% of patients, thereby completely eliminating the need for FVIII coadministration in these patients. If, in the remaining patients, episodic administration of FVIII was required (in total 215 coexposure days with emicizumab and FVIII were reported in 64 patients), most doses of FVIII administered were very low (<0.5 IU/kg bodyweight) and given over a time frame of less than 24 hours. Assuming an even distribution of coexposure events lasting less than 24 hours among patients, this would result in 3.4 exposure days per patient over the course of 6 months. Consistently, no patients from the HAVEN 3 trial (or the HOHOEMI trial) developed new FVIII inhibitors. Compared with data from the INSIGHT study, inhibitors developed with a cumulative incidence of 5.3% after a median of 28 exposure days. It is therefore conceivable that, even in case FVIII concentrates are needed to cope with breakthrough bleeding under treatment with emicizumab, exposure to FVIII is most often limited to less than 24 hours (= 1 exposure day), involves mostly low doses of FVIII, and thereby allows keeping inhibitor development to a minimum.

Further, emicizumab treatment in infants or small children would preclude constant intravenous injections, which presents a great burden of illness and leads to traumatization of young patients. Importantly, early treatment initiation in PUPs may be able to decrease the incidence of intracranial hemorrhage, a potentially fatal complication encountered in infants with impaired hemostasis.

The efficacy of emicizumab prophylaxis has been successfully proven in infants and small children. However, uncertainties about the PK and clinical pharmacology of monoclonal antibodies in pediatric patients remain, with evidence suggesting age-associated PK/PD differences in addition to size-based differences.

Third, an emicizumab-only treatment regimen may just as well be used in patients with inhibitors as prophylaxis with emicizumab has been shown to be superior to prophylaxis with BPA. ABRs under emicizumab have become so low that treatment of breakthrough bleedings with BPA (primarily rFVIIa) seems to be a more reasonable treatment option compared with undergoing inhibitor eradication with ITI.

**Emicizumab versus Immune Tolerance Induction**

Despite the unprecedented efficacy of emicizumab in patients with hemophilia A with or without inhibitors in reducing the rate of bleeding events, doubts about its unrestricted routine use have been expressed.

First, hemophilic patients with inhibitors show both an increased risk of bleeding-associated death and a 70% increase in overall mortality, concluding that inhibitor eradication by ITI should remain the primary goal in this particular patient population. On the other hand, the efficacy of emicizumab is independent of presence of FVIII inhibitors, possibly rendering inhibitor eradication irrelevant. Further, even in the presence of inhibitors, emicizumab significantly reduced the ABR, which may also result in a reduction of mortality.

Second, as mentioned above, treatment of bleeding episodes in hemophilic patients with inhibitors receiving emicizumab is problematic and the procoagulatory potential of concomitant emicizumab and APCC or even rFVIIa yet remains insufficiently studied. However, due to the inferiority of BPA to FVIII with regard to treatment of bleeding episodes and possibly serious adverse events when using APCC in a patient receiving emicizumab, the use of APCC should be avoided as much as possible, which is only feasible when patients undergo inhibitor eradication with ITI.

Another argument in favor of ITI rather than treatment with emicizumab involves a possible future treatment method of hemophilia A—gene therapy. This is discussed below.

Last, the lack of sufficient long-term data regarding efficacy, safety, and immunogenicity precludes the universal application of emicizumab but, on the other hand, warrants generation of more data which will help inform health care treatment decisions.

There are multiple treatment regimens for ITI consisting of high and low FVIII dosing regimens. Patients undergoing high-dose ITI have fewer bleeding events during treatment and achieve tolerance faster, however, high-dose ITI implies an intense treatment schedule and is very expensive. Patients undergoing low-dose ITI bleed more but treatment is less burdensome and more cost-effective.

Prophylactic use of emicizumab may be used in patients undergoing ITI as supportive treatment to minimize bleeding events. This has already been successfully tested and is considered a potential new approach for the management of inhibitor patients.

Subsequently, instead of continued FVIII replacement, patients could be switched to emicizumab-only treatment; however, the question of whether completed ITI necessitates the continued administration of FVIII to maintain tolerance remains unanswered.

Given the quite recent introduction of emicizumab, its use is not included in the 2012 guidelines for the management of hemophilia. Emicizumab’s place in succeeding guidelines will be of interest, given the presence of widely different treatment approaches.

**Q4W Emicizumab Dosing Regimen**

Of the three currently approved dosing intervals, Q4W was associated with higher ABRs of treated bleeding rates (HAVEN 2: 2.2 and HAVEN 4: 2.4). Consistently, increased ABRs were combined with lower PK results (Q4W mean trough level: 38–40 µg/mL), which were, however, expected based on PK simulations and associated with efficacy, similar to those of the other tested dosing intervals. The larger peak–trough fluctuation combined with moderate to high interindividual variability in emicizumab exposure leading to suboptimal emicizumab plasma concentrations may account for increased ABRs of treated bleeds as found in HAVEN 2 and 4. The decision to choose the Q4W dosing regimen, which appeals to both patients and physicians, must be carefully weighed against its potential ABR increase compared with the QW and Q2W regimes and is therefore ultimately chosen based on individual patient preferences.
Emicizumab in Acquired Hemophilia A

While emicizumab has not been approved by health authorities for the treatment of acquired hemophilia A, there are published reports of benefit from treatment with emicizumab. So far, over 15 male and female patients with acquired hemophilia A have been reported to be treated with emicizumab, all of which had excellent response to treatment. The use of emicizumab in this patient population may also offer the option to scale down on the immunosuppressive treatment with corticosteroids to avoid side effects in a typically frail elderly population, and to save the enormous costs of bypassing therapy. A clinical trial with emicizumab and reduced immunosuppression is currently under development (NCT04188639) and is scheduled to start in mid-2020.

Emicizumab in von Willebrand Disease

The bleeding phenotype for the expected persistent complete absence of von Willebrand Disease, as in type 3 von Willebrand disease, together with moderate FVIII-like activity provided by emicizumab remains to be demonstrated.

Economic Considerations

Given the lifelong persistence of hemophilia A, the use of emicizumab greatly depends on its costs. In a cost-effectiveness analysis, emicizumab prophylaxis was associated with fewer bleeding events and increased quality of life at a lower total cost compared with prophylaxis using BPs and no prophylaxis. A study involving a model-based prediction of clinical and economic outcomes confirmed emicizumab’s lower financial impact while at the same time improving patient outcomes. A recent cost-effectiveness analysis, comprising a Markov model and a budget impact model, further substantiates the findings of previous studies.

Novel Therapeutic Options to Treat Hemophilia

Several other novel treatment strategies to combat hemophilia are currently under investigation. One approach to restoring hemostatic balance is by targeting the natural anticoagulant TF pathway inhibitor (TFPI). TFPI is part of the endogenous anticoagulation system and suppresses early stages of coagulation by inhibiting TF-VIIa (non-FIG. 1A) and early forms of prothrombinase. Inhibition of TFPI could lead to increasing procoagulant activity thereby counteracting the anticoagulative nature of hemophilia and achieving hemostatic balance. A phase 1 trial of concizumab, a monoclonal antibody directed against TFPI, showed a favorable safety profile and increased d-dimer levels and prothrombin 1 + 2 fragments in a dose-dependent manner. Phase 2 and 3 trials are currently ongoing.

Another way to induce a more procoagulant state is interference with antithrombin, a central component of the coagulation system. Fitusiran, a novel RNA interference therapy, was able to lower antithrombin levels and increase thrombin generation in patients with hemophilia A or B in a phase 1 dose-escalation study.

A third promising treatment approach for hemophilia A is gene therapy. In a phase 1/2, dose-escalation, safety, tolerability, and efficacy study, nine men with hemophilia A without inhibitors received a single intravenous infusion of a codon-optimized adeno-associated virus serotype 5 (AAV5) vector encoding a B-domain-deleted human FVIII (AAV5-hFVIII-SQ). The study yielded promising results as patients receiving the high dose (6 × 10^13 vector genomes, n = 7) showed FVIII activity of more than 5 IU/dL between weeks 2 and 9, with six of seven patients even reaching normal FVIII activity of >50 IU/dL that were maintained at 1 year after infusion. This potential treatment option is only viable provided no FVIII inhibitors are present, further alluding to a benefit of continued indication for ITI treatment.

Conclusion

Emicizumab is a novel, bispecific antibody that restores the hemostatic balance in patients with hemophilia A irrespective of the presence of inhibitors. Across all three dosage regimens, it impressively reduced the ABR of the majority of patients to zero in several clinical trials. Emicizumab showed a good safety and tolerability profile, but concurrent use of emicizumab and APC could be avoided due to increased risk of TMA and thromboembolic events. Use of emicizumab may be extended to patients with acquired hemophilia A in the future. While additional long-term follow-up data are accumulated, emicizumab is set to revolutionize the treatment of hemophilia A as it unifies both efficacy and practicality compared with other currently available treatment options.

Funding

G.G. is supported by grant SFB54-P04 from the Austrian Science Funds.

Conflict of Interest

B.J. reports grants and personal fees from Roche, during the conduct of the study. P.K. reports personal fees from Roche, during the conduct of the study; grants, personal fees, and nonfinancial support from Baxalta/Shire/Takeda; grants, personal fees, and nonfinancial support from Novo Nordisk; grants, personal fees, and nonfinancial support from CSL Behring; grants, personal fees, and nonfinancial support from ABlynx/Sanoﬁ; and grants from Biotest, outside the submitted work.

References

1 Soucie JM, Evatt B, Jackson D; The Hemophilia Surveillance System Project Investigators. Occurrence of hemophilia in the United States. Am J Hematol 1998;59(04):288–294
2 Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al; Treatment Guidelines Working Group on Behalf of The World Federation Of Hemophilia. Guidelines for the management of hemophilia. Haemophilia 2013;19(01):e1–e47
3 Mannucci PM, Tuddenham EG. The hemophilias—from royal genes to gene therapy. N Engl J Med 2001;344(23):1773–1779
4 Blanchette VS, Key NS, Ljung LR, Mance-Johnson MJ, van den Berg HM, Srivastava A; Subcommittee on Factor VIII. Factor IX and Rare Coagulation Disorders of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Stéphanie E. Abitbol; Thrombosis and Haemostasis Vol. 120 No. 10/2020

Thrombosis and Haemostasis Vol. 120 No. 10/2020

Emicizumab First in Class  Gelbenegger et al.  1367
European Medicines Agency. Assessment report: Hemlibra. January 25, 2018. Available at: https://www.ema.europa.eu/en/documents/assessment-report/hemlibra-epar-public-assessment-report_en.pdf. Accessed June 26, 2020

Kitazawa T, Igawa T, Sampei Z, et al. A bispecific antibody to factors IXa and X restores factor VIII hemostatic activity in a hemophilia A model. Nat Med 2012;18(10):1570–1574

Kitazawa T, Esaki K, Tachibana T, et al. Factor VIIIa-mimetic cofactor activity of a bispecific antibody to factors IXa/X and Xa, emicizumab, depends on its ability to bridge the antigens. Thromb Haemost 2017;117(07):1348–1357

Lenting PJ, Denis CV, Christophe OD. Emicizumab, a bispecific antibody recognizing coagulation factors IX and X: how does it actually compare to factor VIII? Blood 2017;130(23):2463–2468

Blair HA. Emicizumab: a review in haemophilia A. Drugs 2019;79(15):1697–1707

Uchida N, Sambe T, Yoneyama K, et al. A first-in-human phase 1 study of ACE910, a novel factor VIII-mimetic bispecific antibody, in healthy subjects. Blood 2016;127(13):1633–1641

Shima M, Hanabusa H, Taki M, et al. Factor VIII-mimetic function of humanized bispecific antibody in hemophilia A. N Engl J Med 2016;374(21):2044–2053

Pipe SW, Shima M, Lelievre M, et al. Efficacy, safety, and pharmacokinetics of emicizumab prophylaxis given every 4 weeks in people with haemophilia A (HAVEN 4): a multicentre, open-label, non-randomised phase 3 study. Lancet Haematol 2019;6(6):e295–e305

F. Hoffmann-La Roche Ltd. Investigator’s Brochure: Emicizumab. November 2017

Mahlangu J, Oldenburg J, Paz-Priel I, et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med 2018;379(09):811–822

Oldenburg J, Mahlangu JN, Kim B, et al. Emicizumab prophylaxis in hemophilia A with inhibitors. N Engl J Med 2017;377(09):809–818

Young G, Liesner R, Chang T, et al. A multicentre, open-label phase 3 study of emicizumab prophylaxis in children with hemophilia A with inhibitors. Blood 2019;134(24):2127–2138

Genentech Inc. Hemlibra® (emicizumab-kwvh) injection, for subcutaneous use: US prescribing information. Available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=–2483ad8a-fa6b-4d1b-96c5-c195577ed071. Published October 14, 2019

Callaghan M, Negrier C, Paz-Priel I, et al. Emicizumab treatment is efficacious and well tolerated long term in persons with haemophilia A (PwHhA) with or without FVIII inhibitors: pooled data from four HAVEN studies. Paper presented at: ISTH Congress 2019, Melbourne, Australia; July 6–10, 2019

Shima M, Nogami K, Nagami S, et al. A multicentre, open-label study of emicizumab given every 2 or 4 weeks in children with severe haemophilia A without inhibitors. Haemophilia 2019;25(06):979–987

Jiménez-Yuste V, Klamroth R, Castaman G, et al. A single-arm, multicentre, open-label, phase II clinical trial to evaluate the safety and tolerability of prophylactic emicizumab in persons with haemophilia A (PwHHA) with FVIII inhibitors (STASEY): interim analysis results. Paper presented at: ISTH Congress 2019, Melbourne, Australia; July 6–10, 2019

Ebbert PT, Xavier F, Seaman CD, Ragni MV. Emicizumab prophylaxis in patients with haemophilia A with and without inhibitors. Haemophilia 2020;26(01):41–46

Santagostino E, Oldenburg J, Chang T, et al. Surgical experience from four phase III studies (HAVEN 1–4) of emicizumab in persons with haemophilia A (PwHHA) with or without FVIII inhibitors. Paper presented at: ISTH Congress 2019, Melbourne, Australia; July 6–10, 2019

Seaman CD, Ragni MV. Emicizumab use in major orthopedic surgery. Blood Adv 2019;3(11):1722–1724

Biron-Andream CD-CI, Navarro R, Garcia-Gournay C, Theron A, Santagostino E, Schved J-F. Management of surgery in hemophilia A patients with inhibitors during emicizumab prophylaxis. Paper presented at: ISTH Congress 2019, Melbourne, Australia; July 6–10, 2019

Dane KE, Lindsley JP, Streiff MB, Moliterno AR, Khalid MK, Shanbhag S. Successful use of emicizumab in a patient with refractory acquired hemophilia A and acute coronary syndrome requiring percutaneous coronary intervention. Res Pract Thromb Haemost 2019;3(03):420–423

Oldenburg J, Mahlangu JN, Bujan W, et al. The effect of emicizumab prophylaxis on health-related outcomes in persons with haemophilia A with inhibitors: HAVEN 1 Study. Haemophilia 2019;25(01):33–44

Müller J, Pekrul I, Pätzsch B, Berning B, Oldenburg J, Spannagl M. Laboratory monitoring in emicizumab-treated persons with haemophilia A. Thromb Haemost 2019;119(09):1384–1393

Adamkwicz JI, Chen DC, Paz-Priel I. Effects and interferences of emicizumab, a humanised bispecific antibody mimicking activated factor VIII cofactor function, on coagulation assays. Thromb Haemost 2019;119(07):1084–1093

Calatzis AKN, Levy G, Adamkwicz J. Effect of emicizumab – a humanized bispecific antibody mimicking FVIII cofactor function – on a variety of assay systems. Paper presented at: 2016 European Congress on Thrombosis and Haemostasis, Hague, Netherlands; 28–30 September, 2016

Calhoon W, McNerney M, Calatzis A, Chen DC, Adamkwicz J, Morris M. Evaluation of a dedicated calibrator and controls for emicizumab quantification. Paper presented at: THSNA 2018, San Diego, California, United States; March 8–10, 2018

Jenkins PV, Bowyer A, Burgess C, et al. Laboratory coagulation tests and emicizumab treatment A United Kingdom Haemophilia Centre Doctors’ Organisation guideline. Haemophilia 2020;26(01):151–155

Adamkwicz J, Soeda T, Kotani N, Calatzis A, Levy G. Effect of emicizumab (ACE910) – a humanized bispecific antibody mimicking FVIIa cofactor function – on coagulation assays commonly in use for monitoring of hemophilia A patients. Paper presented at: 2017 Scientific Symposium of the Hemostasis and Thrombosis Research Society (HTRS), April 6–8, 2017; Scottsdale, AZ, United States

Yada K, Nogami K, Kashiwagi R, Shima M. A novel hemostatic monitoring system convertible to FVIII activity based on non-activated ROTEM (NATEM) for hemophilia A patients during emicizumab prophylaxis, 2018;32(Suppl 1):3782

Hartmann R, Feenstra T, Valentino L, Dockal M, Scheiflinger F. In vitro studies show synergistic effects of a procoagulant bispecific antibody and bypassing agents. J Thromb Haemost 2018

Nogami K, Matsumoto T, Tabuchi Y, et al. Modified clot waveform analysis to measure plasma coagulation potential in the presence of the anti-factor IXa/factor X bispecific antibody emicizumab. J Thromb Haemost 2018;16(06):1078–1088

Schmitt C, Adamkwicz JI, Xu J, et al. Pharmacokinetics (PK), pharmacodynamics (PD), and PK/PD relationships of emicizumab in persons with hemophilia A (PwHHA) with inhibitors from adolescent/adult (HAVEN 1) and paediatric (HAVEN 2) phase 3 studies. Paper presented at: 11th Annual Congress of the European Association for Haemophilia and Allied Disorders (EAHAD), February 7–9, 2018; Madrid, Spain

Dargaoud Y, Lienhart A, Janbain M, Le Quellec S, Enjalras N, Negrier C. Use of thrombin generation assay to personalize treatment of breakthrough bleeds in a patient with hemophilia and inhibitors receiving prophylaxis with emicizumab. Haematologica 2018;103(04):e181–e183

Levy GG, Asikianus E, Kuebler P, Benchikh El Fegoun S, Esbjerg S, Seremitsis S. Safety analysis of rFVIIa with emicizumab dosing in congenital hemophilia A with inhibitors: experience from the HAVEN clinical program. J Thromb Haemost 2019;17(09):1470–1477
Emicizumab First in Class

Collins PW, Liesner R, Makris M, et al. Treatment of bleeding episodes in haemophilia A complicated by a factor VIII inhibitor in patients receiving Emicizumab. Interim guidance from UKHCDO Inhibitor Working Party and Executive Committee. Haemophilia 2018;24(3):344–347

Susen S, Gruel Y, Godier A, et al. Management of bleeding and invasive procedures in haemophilia A patients with inhibitor treated with emicizumab (Hemlibra®): proposals from the French network on inherited bleeding disorders (MHEMO), the French Reference Centre on Haemophilia, in collaboration with the French Working Group on Perioperative Haemostasis (GHP). Haemophilia 2019;25(5):731–737

Castaman G, Santoro C, Coppola A, et al. Ad hoc Working Group. Emergency management in patients with haemophilia A and inhibitors on prophylaxis with emicizumab: AICE practical guidance in collaboration with SIBioC, SIMEU, SIMEUP, SIPMeL and SIST. Blood Transfus 2020;18(02):143–151

Makris M, Iorio A, Lenting PJ. Emicizumab and thrombosis: The story so far. J Thromb Haemost 2019;17(08):1269–1272

Koelbl P, Thaler J, Jilma-Stohlawetz P, Quehenberger P, Gleixner K, Sperr WR. Emicizumab for the treatment of acquired hemophilia A. Blood 2020. Doi: 10.1182/blood.2020006315

Cortesi PA, Castaman G, Trifirò G, et al. Cost-effectiveness and budget impact of emicizumab prophylaxis in haemophilia A patients with inhibitors. Thromb Haemost 2020;120(02):216–228

Spadarella G, Di Minno A, Milan G, et al. Paradigm shift for the treatment of hereditary haemophilia: towards precision medicine. Blood Rev 2020:39;1232:3511

Batsuli G, Zimowski KL, Tickle K, Meeks SL, Sidonio RF Jr. Immune tolerance induction in paediatric patients with haemophilia A and inhibitors receiving emicizumab prophylaxis. Haemophilia 2019;25(05):789–796

Carcao M, Escuriola-Ettighausen C, Santagostino E, et al; Future of Immunotolerance Treatment Group. The changing face of immune tolerance induction in haemophilia A with the advent of emicizumab. Haemophilia 2019;25(04):676–684

Yoneyama K, Schmitt C, Kotani N, et al. A pharmacometric approach to substitute for a conventional dose-finding study in rare diseases: example of phase III dose selection for emicizumab in hemophilia A. Clin Pharmacokinet 2018;57(09):1123–1134

Al-Banaa K, Alhillan A, Hawa F, et al. Emicizumab use in treatment of acquired hemophilia A: a case report. Am J Case Rep 2019;20:1046–1048

Möhne P, Pekrl I, Spannagl M, Sturm A, Singh D, Dechant C. Emicizumab in the treatment of acquired haemophilia: a case report. Transfus Med Hemother 2019;46(02):121–123

Koelbl P, Sperr W, Schellongowski P, et al. Emicizumab for the treatment of acquired hemophilia A: lessons learned from 4 very different cases. Blood 2018;132(Suppl 1):2476

Koelbl P, Thaler J, Jiima-Stohlawetz P, Quehenberger P, Gleixner K, Sperr WR. Emicizumab for the treatment of acquired hemophilia A. Blood 2020. Doi: 10.1182/blood.2020006315

Weyand AC, Flood VH, Shavit JA, Pipe SW. Efficacy of emicizumab in a pediatric patient with type 3 von Willebrand disease and alloantibodies. Blood Adv 2019;3(18):2748–2750

ICER. Emicizumab for hemophilia A with inhibitors: effectiveness and value. April 16, 2018. Available at: https://icer-review.org/wp-content/uploads/2017/08/ICER_Hemophilia_Final_Evidence_Report_041618.pdf. Accessed June 26, 2020

Mahajerin A, Zhou Z-Y, Raimundo K, et al. Model of short and long-term outcomes of emicizumab prophylaxis treatment for persons with hemophilia A. Blood 2018;132(Suppl 1):3511

Möhnle P, Pekrul I, Spannagl M, Sturm A, Singh D, Dechant C. Prevention and management of bleeding episodes in patients with acquired hemophilia A. Drugs 2018;78(18):1861–1872

Koelbl P, Sperr W, Schellongowski P, et al. Emicizumab for the treatment of acquired hemophilia A: lessons learned from 4 very different cases. Blood 2018;132(Suppl 1):2476

Koelbl P, Thaler J, Jiima-Stohlawetz P, Quehenberger P, Gleixner K, Sperr WR. Emicizumab for the treatment of acquired hemophilia A. Blood 2020. Doi: 10.1182/blood.2020006315

Cortesi PA, Castaman G, Trifirò G, et al. Cost-effectiveness and budget impact of emicizumab prophylaxis in haemophilia A patients with inhibitors. Thromb Haemost 2020;120(02):216–228

Spadarella G, Di Minno A, Milan G, et al. Paradigm shift for the treatment of hereditary haemophilia: towards precision medicine. Blood Rev 2020:39;100618

Peterson JA, Maroney SA, Mast AE. Targeting TFPI for hemophilia treatment. Thromb Res 2016;141(Suppl 2):S28–S30

Cowdary P, Lethagen S, Friedrich U, et al. Safety and pharmacokinetics of anti-TFPI antibody (conizumab) in healthy volunteers and patients with hemophilia: a randomized first human dose trial. J Thromb Haemost 2015;13(05):743–754

Pasi KJ, Rangarajan S, Georgiev P, et al. Targeting of antithrombin in hemophilia A or B with RNAi therapy. N Engl J Med 2017;377(09):819–828

Rangarajan S, Walsh L, Lester W, et al. AAV5-factor VIII gene transfer in severe hemophilia A. N Engl J Med 2017;377(26):2519–2530