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Real-World Safety of Emicizumab: The First Interim Analysis of the European Haemophilia Safety Surveillance (EUHASS) Database

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Disclosures

AS: employee of and holder of stocks/shares in F. Hoffmann-La Roche Ltd; **NSB:** employee of F. Hoffmann-La Roche Ltd; **RG:** employee of F. Hoffmann-La Roche Ltd, recent employee of Britannia Pharmaceuticals, and holder of stocks/shares in Ravi Gadiraju Pharma Ltd; **TC:** employee of and holder of stocks/shares in Genentech, Inc.; **MH:** employee of Roche Canada, holder of stocks/shares in F. Hoffmann-La Roche Ltd, and a recent employee of PRO Unlimited.

Key takeaways

- Among persons with hemophilia A treated with emicizumab at centers participating in EUHASS, 2 adverse events were reported and there were no cases of thrombotic microangiopathy or anaphylaxis during 2018
- No new or emerging safety signals for emicizumab were identified

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The EUHASS registry collects real-world safety data on the use of emicizumab in a broad, representative population of PwHA

Background

- **Long-term data** from the HAVEN 1–4 clinical trials **reaffirmed the safety and efficacy of emicizumab prophylaxis** in PwHA[1]
- However, early data from the first phase III trial (HAVEN 1[2]) identified a **risk for TE or TMA when emicizumab was concomitantly administered with aPCC** (average cumulative dose of >100 U/kg per 24 hours for ≥24 hours)
  - A Black box warning[3] and risk minimization strategies were subsequently instituted
- **EUHASS** is a large pharmacovigilance program dedicated to **monitoring the safety of treatments** in those with inherited bleeding disorders, providing data relating to safety events reported for approved drugs[4]
  - EUHASS provides annual reports of AEs reported for PwHA taking emicizumab in the real-world setting

Objective: To summarize TE, TMA, anaphylaxis, and other AEs reported to EUHASS in association with emicizumab prophylaxis

AE, adverse event; aPCC, activated prothrombin complex concentrate; EUHASS, European Haemophilia Safety Surveillance; PwHA, persons with hemophilia A; TE, thrombotic event; TMA, thrombotic microangiopathy.

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2. Oldenburg J, et al. *N Engl J Med* 2017;377:809–18;
3. Food and Drug Administration. Hemlibra® Prescribing Information, 2020 https://www.gene.com/download/pdf/hemlibra_prescribing.pdf. Accessed November 02, 2020;
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This interim analysis summarizes TE, TMA, and anaphylaxis events reported concomitant to emicizumab use during 2018

Study design

- EUHASS: A European pharmacovigilance program that monitors AEs in hemophilia and other blood-related disorders
  - AEs are submitted electronically (in English) quarterly or at the time of its occurrence to the EUHASS website
  - While a report of an AE prompts asking for pre-defined questions, EUHASS does not have the ability to systematically collect follow-up information (to understand the context of an AE and subsequent outcomes)
  - After each complete year of surveillance, participating centers provide data on registered patients and their treatments*
- 86 participating hemophilia centers across 27 European countries†

Study population

- All PwHA receiving emicizumab prophylaxis at participating sites in the EUHASS registry during 2018

Endpoints‡

- Number and proportion of PwHA exposed to emicizumab (with or without concomitant administration of aPCC, rFVIIa, or FVIII) with TE, TMA, anaphylaxis, other AEs, and unexpected poor efficacy§
- Description of individual cases of TE and TMA

*The Sponsor receives emicizumab annual reports generated by EUHASS 12–14 months following each calendar year; †Participating countries: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Latvia, Lithuania, Malta, The Netherlands, Poland, Portugal, Romania, Russia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom; centers reported information on all PwHA treated, therefore minimizing selection bias; ‡Endpoints are provided as descriptive statistics; §EUHASS AE data are not collected according to MedDRA classification; however, events were coded at MedDRA preferred term level as far as possible.

AE, adverse event; aPCC, activated prothrombin complex concentrate; EUHASS, European Haemophilia Safety Surveillance; FVIII, factor VIII; MedDRA, Medical Dictionary for Regulatory Activities; PwHA, persons with hemophilia A; rFVIIa, recombinant activated factor VIIa; TE, thrombotic event; TMA, thrombotic microangiopathy.

EUHASS collected data from 148 PwHA treated with emicizumab during 2018

- Data from 148 PwHA receiving emicizumab in 2018 were reported and included in this interim analysis
- Concomitant treatments included aPCC, rFVIIa, and FVIII products

Hemophilia centers and people treated	n or n (%)
Number of reporting centers	69
People treated with emicizumab with/without other treatments	148
People treated with emicizumab only	115 (77.7)
People treated with emicizumab + aPCC	1 (0.7)
People treated with emicizumab + rFVIIa	23 (15.5)
People treated with emicizumab + FVIII*	9 (6.1)

*FVIII treatment did not include recombinant porcine FVIII.

aPCC, activated prothrombin complex concentrate; FVIII, factor VIII; PwHA, persons with hemophilia A; rFVIIa, recombinant activated factor VIIa.

Two AEs concomitant to emicizumab use were reported in 2018

Event	PwHA receiving emicizumab only (n=115)	PwHA receiving emicizumab + aPCC (n=1)	PwHA receiving emicizumab + rFVIIa (n=23)	PwHA receiving emicizumab + FVIII (n=9)
Anaphylaxis	0	0	0	0
Allergic or other acute reaction	1	0	0	0
Unexpected poor efficacy	0	0	0	0
Transfusion-transmitted infection	0	0	0	0
Inhibitor* event				
First occurrence of inhibitor development	0	0	0	0
Recurrence of inhibitors	0	0	0	0
TMA	0	0	0	0
Thrombosis within 30 days of receiving treatment	0	1	0	0

*Inhibition due to anti-FVIII antibody.

AE, adverse event; aPCC, activated prothrombin complex concentrate; FVIII, factor VIII; PwHA, persons with hemophilia A; rFVIIa, recombinant activated factor VIIa; TMA, thrombotic microangiopathy.

One event each of TE and acute reaction was reported for PwHA taking emicizumab

One event of TE

- **Myocardial infarction** was reported for a >65-year-old male 10 hours after dosing with emicizumab + aPCC
- Frequency of occurrence: 0.7% (n=1/148 PwHA; 95% CI: 0.02%–3.71%)

One event of acute reaction

- An **acute reaction (rash)** was reported for a male 48 hours after dosing with emicizumab, who later recovered. The AE was considered by the investigator to be probably related to concentrate*
- Frequency of occurrence: 0.7% (n=1/148 PwHA; 95% CI: 0.02%–3.71%)

No events of TMA, anaphylaxis, or unexpected poor efficacy were reported to EUHASS

*Since EUHASS lists ‘concentrate’ for all reported AEs and emicizumab was the only treatment reported for this PwHA, ‘concentrate’ probably refers to emicizumab.

AE, adverse event; aPCC, activated prothrombin complex concentrate; CI, confidence interval; EUHASS, European Haemophilia Safety Surveillance; PwHA, persons with hemophilia A; TE, thrombotic event; TMA, thrombotic microangiopathy.

Limitations of EUHASS registry data and of this interim analysis

- Emicizumab annual reports generated by EUHASS are received by the sponsor 12–14 months following each calendar year; as such, a time lag exists between reported AEs and availability of this information
- Although EUHASS followed up with and confirmed the accuracy of AEs reported at participating sites, some detailed information on the reported AEs is missing, highlighting that more comprehensive reporting of AEs is required, especially in the era of novel therapies
- This analysis was limited by the low number of emicizumab-treated PwHA – especially in those without FVIII inhibitors, and relatively short follow-up time in this data cut; however, these limitations will be addressed through future data cuts
- Since this interim analysis assumes concomitant administration of emicizumab and other treatments, the results presented are conservative and may overestimate annual TE and TMA incidence in PwHA receiving emicizumab with a coagulation factor product

AE, adverse event; EUHASS, European Haemophilia Safety Surveillance; FVIII, factor VIII; PwHA, persons with hemophilia A; TE, thrombotic event; TMA, thrombotic microangiopathy.

Conclusions

Among PwHA treated with emicizumab at centers participating in EUHASS, 2 AEs were reported and there were no cases of TMA, anaphylaxis, or unexpected poor efficacy during 2018

Despite the limitations of the registry data, these interim real-world data suggest consistency with the AE profile of emicizumab in clinical trials. A full assessment is reserved for the final analysis

No new or emerging safety signals for emicizumab were identified

AE, adverse event; EUHASS, European Haemophilia Safety Surveillance; PwHA, persons with hemophilia A; TMA, thrombotic microangiopathy.

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