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# Real-world Outcomes of Emicizumab in Hemophilia A with or without FVIII Inhibitors from the Canadian Hemophilia Bleeding Disorder Registry

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## Summary

Analysis of **146 people with hemophilia A (PwHA)** in the Canadian Bleeding Disorders Registry **receiving emicizumab** prior to December 2021

**Three adverse events**, and no thrombotic events or thrombotic microangiopathies, were **reported in 2021**

These data can inform healthcare practitioners and regulatory authorities about the **real-world safety** and **effectiveness** of **emicizumab** in PwHA

**76.7% of patients had no recorded bleeds;** a substantial decrease in bleeds was seen following emicizumab treatment

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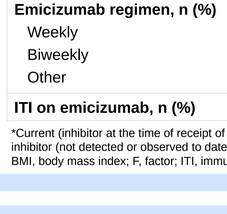
## Background

- Hemophilia A is a bleeding disorder characterized by deficiency of blood coagulation factor (F)VIII, which leads to lifelong bleeding tendency.
- The Canadian Bleeding Disorders Registry (CBDR) is designed to assist clinicians with the management of people with bleeding disorders, and contains routinely collected information on people with hemophilia A (PwHA) in Canada.
- We used CBDR data to evaluate the effectiveness, safety, and treatment patterns of emicizumab, a bispecific antibody therapy approved for use in PwHA in Canada.[1]

## Methods: Data from people receiving emicizumab prophylaxis in the CBDR database was analysed for safety and efficacy outcomes

**Figure 1. Analysis of the CBDR database for PwHA receiving emicizumab**




Retrieved de-identified data of all registered PwHA who received emicizumab at least once prior to **December 31, 2021**.

**Baseline demographics** stratified by disease severity

**Efficacy outcomes:** measured by proportion of PwHA with zero, traumatic, spontaneous, or joint bleeds, annualized bleeding rates* (ABRs) for any treated bleed, Hemophilia Joint Health Score (HJHS), Patient Reported Outcomes Burdens and Experiences (PROBE), and EQ-5D index and visual analog scale (VAS) scores.

We performed a **complete data analysis**, without imputation.
Intra-patient comparisons of ABRs before and after emicizumab treatment were done using a negative binomial regression model.

This study was approved by the ethics board of McMaster University and other participating centers and abides by the principles of the Declaration of Helsinki.

*ABRs were calculated as (total number of bleeds/duration of follow-up [days])*365.25.

## Baseline demographics: 146 PwHA received emicizumab at least once up to December 2021 in the CBDR database

- The median (Q1–Q3) age at initiation of emicizumab was 13.9 (6.7–28.7) years; 58.9% (n=86) of PwHA were ≤18 years.
- The majority of PwHA had severe disease (**Table 1**).

**Table 1. Baseline characteristics of PwHA who received emicizumab at least once prior to December 31, 2021, overall and by disease severity**

| | Overall (N=146) | Severe† (n=132) | Moderate† (n=10) | Mild† (n=4) |
|---|---|---|---|---|
| **Male, n (%)** | 145 (99.3) | 131 (99.2) | 10 (100.0) | 4 (100.0) |
| **BMI, mean ± SD kg/m², n** | 23.0 ± 9.8, 104 | 22.9 ± 10.1, 93 | 25.2 ± 6.5, 8 | 18.6 ± 4.4, 3 |
| **Age, years** | | | | |
| Mean ± SD, n | 21.1 ± 20.1, 146 | 19.6 ± 18.9, 132 | 38.4 ± 28.3, 10 | 25.5 ± 16.1, 4 |
| Median (Q1–Q3) | 13.9 (6.7–28.7) | 12.6 (4.8–27.0) | 30.2 (13.3–62.2) | 21.3 (14.2–36.8) |
| **FVIII inhibitor status,* n (%)** | | | | |
| Current | 59 (40.4) | 52 (39.4) | 4 (40.0) | 3 (75.0) |
| Inhibitor history | 22 (15.1) | 19 (14.4) | 2 (20.0) | 1 (25.0) |
| No inhibitor | 65 (44.5) | 61 (46.2) | 4 (40.0) | 0 |
| **Emicizumab regimen, n (%)** | | | | |
| Weekly | 94 (64.4) | 85 (64.4) | 7 (70.0) | 2 (50.0) |
| Biweekly | 38 (26.0) | 33 (25.0) | 3 (30.0) | 2 (50.0) |
| Other | 14 (9.6) | 14 (10.6) | 0 | 0 |
| **ITI on emicizumab, n (%)** | 6 (4.1) | 6 (4.5) | 0 | 0 |

*Current (inhibitor at the time of receipt of the first dose of emicizumab); history of FVIII inhibitor (inhibitor detected prior to emicizumab but no current inhibitor); no inhibitor (not detected or observed to date). †Severe (FVIII < 0.01IU/mL), moderate (0.01 ≤ FVIII ≤ 0.05IU/mL), and mild (0.05 < FVIII ≤ 0.40IU/mL).
BMI, body mass index; F, factor; ITI, immune tolerance induction; Q, quartile; SD, standard deviation.

## Safety: Three adverse events, and no TEs or TMAs, were reported by PwHA in 2021

- Three adverse events were reported by PwHA in 2021, including two allergic reactions and one case of large hematoma at the operative site following removal of a port-a-cath
  - The case of large hematoma was reported among traumatic bleeds.
- No thromboembolisms (TEs) or thrombotic microangiopathies (TMAs) occurred.

## Efficacy: PwHA reported favorable efficacy outcomes of emicizumab, including a majority with zero bleeds over a median follow-up of >1 year

- Over a median follow-up of 389 days, 76.7% (n=112) of PwHA treated with emicizumab had no recorded bleeds (**Table 2**).
- Effectiveness was consistent irrespective of severity of hemophilia A and FVIII inhibitor status; outcomes are shown in **Table 2** and **Table 3**, respectively.

**Table 2. Effectiveness outcomes in PwHA who received emicizumab at least once prior to December 31, 2021, by disease severity**

| Outcomes | Overall (N=146) | Severe (n=132) | Moderate (n=10) | Mild (n=4) |
|---|---|---|---|---|
| **Zero bleeds, n (%)** | 112 (76.7) | 104 (78.8) | 5 (50.0) | 3 (75.0) |
| **Traumatic bleeds, n (%)** | 18 (12.3) | 16 (12.1) | 1 (10.0) | 1 (25.0) |
| **Spontaneous bleeds, n (%)** | 19 (13.0) | 15 (11.4) | 3 (30.0) | 1 (25.0) |
| **Joint bleeds, n (%)** | 13 (8.9) | 12 (9.1) | 0 | 1 (25.0) |
| **ABR, median (Q1–Q3), n** | 0.0 (0.0–0.0), 146 | 0.0 (0.0–0.0), 132 | 0.2 (0.0–0.9), 10 | 0.0 (0.0–4.4), 4 |
| **Follow-up median, days, (Q1–Q3), n** | 389 (57–799), 146 | 367 (48.0–809.0), 132 | 604 (427.0–749.0), 10 | 442 (329.5–949.5), 4 |
| **ABR, median (Q1–Q3), n (PwHA with bleeds)** | 1.0 (0.5–2.0), 34 | 1.0 (0.4–1.8), 28 | 0.9 (0.8–2.0), 5 | 8.8 (8.8–8.8), 1 |
| **Follow-up days, median (Q1–Q3), n (PwHA with bleeds)** | 711 (400–889), 34 | 730 (387.5–917.5), 28 | 714 (477.0–749.0), 5 | 541 (541.0–541.0), 1 |
| **HJHS score, mean ± SD, n** | 12.5 ± 16.0, 36 | 13.2 ± 16.6, 32 | 1.7 ± 2.9, 3 | 20.7 ± NE, 1 |
| **PROBE score, mean ± SD, n** | 0.8 ± 0.2, 12 | 0.8 ± 0.2, 9 | 0.6 ± NE, 1 | 0.9 ± 0.0, 2 |
| **EQ-5D score, mean ± SD, n** | 0.8 ± 0.2, 12 | 0.7 ± 0.2, 9 | 0.6 ± NE, 1 | 0.9 ± 0.0, 2 |
| **EQ-5D VAS score, mean ± SD, n** | 75.8 ± 16.6, 4 | 81.0 ± 15.7, 3 | 60.0 ± NE, 1 | NE, 0 |

**Table 3. Effectiveness outcomes in PwHA who received emicizumab at least once prior to December 31, 2021, by inhibitor status**

| Outcomes | Current (n=59) | History (n=22) | No inhibitor (n=65) |
|---|---|---|---|
| **Zero bleeds, n (%)** | 39 (66.1) | 20 (90.9) | 53 (81.5) |
| **Traumatic bleeds, n (%)** | 11 (18.6) | 0 | 7 (10.8) |
| **Spontaneous bleeds, n (%)** | 12 (20.3) | 0 | 7 (10.8) |
| **Joint bleeds, n (%)** | 9 (15.3) | 0 | 4 (6.2) |
| **ABR, median (Q1–Q3), n** | 0.0 (0.0–0.4), 59 | 0.0 (0.0–0.0), 22 | 0.0 (0.0–0.0), 65 |
| **Follow-up days, median (Q1–Q3), n** | 837 (541–932), 59 | 354 (52–715), 22 | 59 (32–350), 65 |
| **ABR, median (Q1–Q3), n (PwHA with bleeds)** | 0.9 (0.4–1.6), 20 | 0.5 (0.4–0.5), 2 | 3.9 (0.9–10.0), 12 |
| **Follow-up days, median (Q1–Q3), n (PwHA with bleeds)** | 848 (643–937), 20 | 805 (749–861), 2 | 439 (56–643), 12 |
| **HJHS score, mean ± SD, n** | 18.2 ± 18.2, 20 | 1.8 ± 3.5, 4 | 6.5 ± 10.0, 12 |
| **PROBE score, mean ± SD, n** | 0.8 ± 0.2, 9 | 0.7 ± 0.1, 2 | 0.9 ± NE, 1 |
| **EQ-5D score, mean ± SD, n** | 0.7 ± 0.2, 9 | 0.8 ± 0.2, 2 | 0.9 ± NE, 1 |
| **EQ-5D VAS score, mean ± SD, n** | 81.0 ± 15.7, 3 | 60.0 ± NE, 1 | NE, 0 |

Participants could report multiple types of bleed; other bleed types were included in the total patient population but not itemized. The PROBE score can range from 0 (worst health status) to 1 (best health status). The EQ-5D utility index can range from -0.28 (worst health status) to 1 (best health status). The EQ-5D VAS can range from 0 (worst health status) to 100 (best health status). The HJHS can range from 0 (best health status) to 124 (worst health status). *Current (inhibitor at the time of receipt of the first dose of emicizumab); history of FVIII inhibitor (inhibitor detected prior to emicizumab but no current inhibitor); no inhibitor (not detected or observed to date). HJHS, Hemophilia Joint Health Score; NE, not estimable; PROBE, Patient Reported Outcomes Burdens and Experiences; VAS, visual analog scale.

## Analysis: Before–after comparisons showed decreases in ABRs following emicizumab initiation

- Intra-patient comparisons of ABRs before and after emicizumab treatment were done using a negative binomial regression model
- Before-after comparison in all PwHA showed a decrease in mean (95% confidence interval [CI]) ABR from **2.38 (1.77–3.22) pre-emicizumab** (2018, prior to first dose) to **0.36 (0.24–0.53) post-emicizumab** (rate ratio [RR] 0.15, p<0.0001).
- In PwHA with bleeds before or after initiation of emicizumab (n=97), mean (95% CI) ABR decreased from **5.31 (3.79–7.45) pre-emicizumab** to **0.87 (0.58–1.32) post-emicizumab** (RR 0.16, p<0.0001).

## Conclusions

- This analysis describes the baseline characteristics, bleed outcomes, and safety for PwHA treated with emicizumab before December 31, 2021, in Canada.
- The majority had severe disease and current or historical FVIII inhibitors.
- The data show that 76.7% of PwHA had no recorded bleeds and there was a substantial decrease in bleeds post-emicizumab, with an overall median ABR of 0.0 (n=146).

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Emicizumab is subject to additional safety monitoring requirements in many countries. Healthcare professionals are asked to report any suspected adverse reactions to the regulatory authorities in your country according to your national requirements.

**References**

1. Hemlibra Product Monograph. Available from: https://www.rochecanada.com/PMs/Hemlibra/Hemlibra_PM_E.pdf, accessed Nov 2021.

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