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Experience with Emicizumab Among People with Hemophilia A in the Canadian Hemophilia Bleeding Disorders Registry

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Summary

A total of 533 people with hemophilia A (PwHA) received emicizumab at least once prior to December 31, 2022. Since last year's report, 387 new PwHA have been exposed to emicizumab

Twenty-two new adverse events were experienced in the 533 PwHA exposed to emicizumab. This included one event of thrombosis (occurring in one person with COVID-19)

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

Following emicizumab treatment, a substantial decrease in bleeds was observed in both inhibitor and non-inhibitor participants over a median follow-up of 36 weeks. Overall, **73% of participants had no recorded bleeds**

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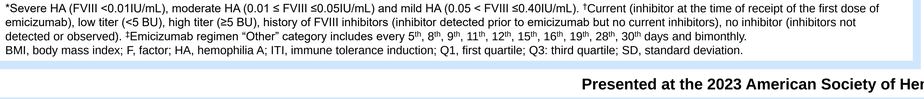
Background

- The use of emicizumab as prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes in congenital hemophilia A (HA) was approved by Health Canada for the treatment of people with HA (PwHA) with factor (F)VIII inhibitors in 2018, and without FVIII inhibitors in 2019.[1]
- Here, we present the results of a non-interventional cohort study, using data routinely collected by the Canadian Bleeding Disorders Registry (CBDR) to evaluate treatment patterns of emicizumab in Canada and the associated safety and effectiveness outcomes, including quality of life; this presentation summarizes the cumulative experience with emicizumab of PwHA registered in the CBDR up to December 31, 2022.

Methods

- De-identified data were extracted from the CBDR database for all registered PwHA who had received emicizumab at least once prior to December 31, 2022.
- Baseline demographic characteristics were stratified by disease severity (defined by the level of endogenous FVIII activity) and age.
- Effectiveness outcomes were measured by the proportion of PwHA with zero, traumatic, spontaneous, or joint bleeds as well as annualized bleeding rates (ABRs) for all bleeds. Intra-patient comparisons of bleeding were performed, using a negative binomial regression model, for all PwHA and for those with ≥6 months of follow-up in both pre- and post-emicizumab periods as a sensitivity analysis.
- Effectiveness outcomes also included participants' 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.
- This study was approved by the research ethics board of McMaster University and other participating centers and abides by the guiding principles of the Declaration of Helsinki.

Figure 1. Overview of the study cohort using data collected by the CBDR: Year 4 results are presented here.



CBDR, Canadian Bleeding Disorders Registry; PwHA, people with hemophilia A.

A total of 533 PwHA received at least one dose of emicizumab (PwHAE) in the CBDR database prior to December 31, 2022

- Overall, 498 (93.4%) PwHAE (including two females) had severe disease, 28 (5.3%) had moderate disease, and 7 (1.3%) had mild disease (**Table 1**).
- At the start of emicizumab exposure (**Table 1**): 220 (41.3%) PwHAE were <18 years old, 78 (14.6%) PwHAE had current FVIII inhibitors, 82 (15.4%) had a history of FVIII inhibitors, and 373 (70.0%) had no history of FVIII inhibitors.

Table 1. Baseline characteristics and emicizumab regimen overall, and by disease severity and age group.

Characteristic	Overall	Severity of Hemophilia A*			Age	
		Severe	Moderate	Mild	<18 years	≥18 years
N (%)	533	498 (93.4)	28 (5.3)	7 (1.3)	220 (41.3)	313 (58.7)
Age, years						
Mean ± SD, n	25.2 ± 18.0, 533	24.8 ± 17.5, 498	32.4 ± 23.6, 28	27.8 ± 24.1, 7	8.9 ± 5.1, 220	36.7 ± 14.6 313
Median (Q1, Q3)	21.1 (10.6, 37.0)	21.2 (10.5, 36.8)	26.9 (13.0, 47.9)	17.0 (10.4, 48.0)	9.1 (4.5, 13.1)	34.3 (24.7, 46.0)
Male, n (%)	531/533 (99.6)	496/498 (99.6)	28/28 (100.0)	7/7 (100.0)	219/220 (99.5)	312/313 (99.7)
Mean BMI (kg/m²) ± SD, n	23.8 ± 9.5, 424	23.8 ± 9.3, 393	25.9 ± 12.4, 27	17.3 ± 4.5, 4	19.7 ± 10.0, 191	27.3 ± 7.5, 233
FVIII inhibitor status†, n (%)						
Current	78/533 (14.6)	67/498 (13.5)	5/28 (17.9)	6/7 (85.7)	38/220 (17.3)	40/313 (12.8)
Low titer	44/533 (8.3)	38/498 (7.6)	3/28 (10.7)	3/7 (42.9)	22/220 (10.0)	22/313 (7.0)
High titer	34/533 (6.4)	29/498 (5.8)	2/28 (7.1)	3/7 (42.9)	16/220 (7.3)	18/313 (5.8)
Inhibitor history	82/533 (15.4)	77/498 (15.5)	4/28 (14.3)	1/7 (14.3)	25/220 (11.4)	57/313 (18.2)
No inhibitor	373/533 (70.0)	354/498 (71.1)	19/28 (67.9)	0/7 (0.0)	157/220 (71.4)	216/313 (69.0)
Emicizumab regimen, n (%)						
Weekly	260/533 (48.8)	241/498 (48.4)	15/28 (53.6)	4/7 (57.1)	76/220 (34.5)	184/313 (58.8)
Biweekly	229/533 (43.0)	216/498 (43.4)	10/28 (35.7)	3/7 (42.9)	121/220 (55.0)	108/313 (34.5)
Other‡	44/533 (8.3)	41/498 (8.2)	3/28 (10.7)	0/7 (0.0)	23/220 (10.5)	21/313 (6.7)
ITI while on emicizumab, n (%)	6/533 (1.1)	6/498 (1.2)	0/28 (0.0)	0/7 (0.0)	5/220 (2.3)	1/313 (0.3)

*Severe HA (FVIII <0.01IU/mL), moderate HA (0.01 ≤ FVIII ≤0.05IU/mL) and mild HA (0.05 < FVIII ≤0.40IU/mL). †Current (inhibitor at the time of receipt of the first dose of emicizumab), low titer (<5 BU), high titer (≥5 BU), history of FVIII inhibitors (inhibitor detected prior to emicizumab but no current inhibitors), no inhibitor (inhibitors not detected or observed). ‡Emicizumab regimen "Other" category includes every 5th, 8th, 9th, 11th, 12th, 15th, 16th, 19th, 28th, 30th days and bimonthly.
BMI, body mass index; F, factor; HA, hemophilia A; ITI, immune tolerance induction; Q1, first quartile; Q3: third quartile; SD, standard deviation.

The safety profile of emicizumab is consistent with previous reports

- A total of 22 adverse events (AEs) were reported during the entire observation period, nine of which were cases of COVID-19.
- The other 13 AEs comprised an event of thrombosis (occurring in one person with COVID-19), seven allergic reactions, two incidences of FVIII inhibitor development, two neurological events (headache; headache, nausea, and vomiting) and one case of a large hematoma that developed at an operative site following removal of a port-a-cath
  - The event of thrombosis was considered by the clinician to be possibly related to the use of emicizumab; it was judged to be device-associated and occurred in a patient who had undergone surgery within three months prior to the event.
- There were no discontinuations or dose modifications due to AEs.

PwHA reported favorable effectiveness outcomes for emicizumab

- Over a median (Q1, Q3) follow-up time of 249 (136, 395) days, 388 (72.8%) PwHAE had no recorded bleeds (**Table 2**).

Table 2. Effectiveness outcomes in PwHA who received emicizumab at least once prior to December 31, 2022, by disease severity and inhibitor status.

Effectiveness outcomes	Overall	Severity of hemophilia A*			Inhibitor status†		
		Severe	Moderate	Mild	Current	History	No inhibitor
N	533	498	28	7	78	82	373
Zero bleeds, n (%)	388 (72.8)	363 (72.9)	19 (67.9)	6 (85.7)	49 (62.8)	64 (78.0)	275 (73.7)
Traumatic bleeds, n (%)	87 (16.3)	83 (16.7)	3 (10.7)	1 (14.3)	16 (20.5)	7 (8.5)	64 (17.2)
Spontaneous bleed, n (%)	69 (12.9)	63 (12.7)	5 (17.9)	1 (14.3)	15 (19.2)	8 (9.8)	46 (12.3)
Joint bleeds, n (%)	106 (19.9)	100 (20.1)	5 (17.9)	1 (14.3)	21 (26.9)	12 (14.6)	73 (19.6)
ABR‡, median (Q1, Q3), n all PwHA	0.0 (0.0, 0.4), 533	0.0 (0.0, 0.4), 498	0.0 (0.0, 0.5), 28	0.0 (0.0, 0.0), 7	0.0 (0.0, 0.5), 78	0.0 (0.0, 0.0), 82	0.0 (0.0, 0.7), 373
Follow-up days for all PwHA, median (Q1, Q3), n	249 (136, 395), 533	248 (141, 393), 498	246 (67, 682), 28	681 (264, 906), 7	1067 (408, 1268), 78	238 (129, 396), 82	221 (128, 312), 373
ABR‡, median (Q1, Q3), n PwHA with bleeds	2.1 (1.1, 4.8), 145	2.1 (1.1, 4.7), 135	1.9 (0.6, 9.4), 9	6.0 (6.0, 6.0), 1	1.0 (0.4, 1.6), 29	1.7 (0.9, 4.3), 18	3.0 (1.5, 6.2), 98
Follow-up days for PwHA with bleeds, median (Q1, Q3), n	302 (218, 425), 145	298 (220, 410), 135	571 (47, 1079), 9	906 (906, 906), 1	1072 (571, 1254), 29	322 (236, 425), 18	264 (184, 354), 98
HJHS§ mean ± SD, n	9.4 ± 13.3, 76	9.6 ± 13.7, 69	5.8 ± 7.8, 5	12.4 ± 16.1, 2	17.8 ± 17.5, 22	7.6 ± 12.4, 16	5.3 ± 7.9, 38
PROBE score§, mean ± SD, n	0.8 ± 0.2, 59	0.8 ± 0.2, 53	0.6 ± 0.1, 4	0.9 ± 0.0, 2	0.7 ± 0.2, 14	0.8 ± 0.1, 8	0.8 ± 0.2, 37
EQ-5D index score§, mean ± SD, n	0.8 ± 0.2, 59	0.8 ± 0.2, 53	0.8 ± 0.1, 4	0.9 ± 0.0, 2	0.8 ± 0.2, 14	0.8 ± 0.1, 8	0.8 ± 0.2, 37
EQ-5D VAS score§, mean ± SD, n	77.0 ± 16.3, 59	77.7 ± 16.4, 53	64.1 ± 13.4, 4	85.0 ± 7.1, 2	75.6 ± 19.4, 14	71.8 ± 9.6, 8	78.7 ± 16.3, 37

*Severe HA (FVIII <0.01IU/mL), moderate HA (0.01 ≤ FVIII ≤0.05IU/mL) and mild HA (0.05 < FVIII ≤0.40IU/mL). †Current (inhibitor at the time of receipt of the first dose of emicizumab), history of FVIII inhibitors (inhibitors detected prior to emicizumab but no current inhibitors), no inhibitor (no inhibitors detected or observed yet). ‡Calculated as: (total number of bleeds/duration of follow-up [days])×365.25 for PwHA who received emicizumab prior to December 31, 2022. §The HJHS can range from 0 (normal) to 124 (worst joint status). 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).
ABR, annualized bleeding rate; F, factor; HA, hemophilia A; HJHS, Hemophilia Joint Health Score; PROBE, Patient Reported Outcomes Burdens and Experiences; PwHA, people with hemophilia A; Q1, quartile 1; Q3, quartile 3; SD, standard deviation; VAS, visual analog scale.

Effectiveness outcomes after switching to emicizumab: comparison of pre- and post-emicizumab periods

- Using a negative binomial regression model, an intra-patient comparison in all PwHAE (n=533) showed a decrease in mean (95% confidence interval [CI]) ABR from 1.22 (1.06–1.42), pre-emicizumab (2018, prior to first dose) to 0.50 (0.41–0.60) post-emicizumab (rate ratio [95% CI] 0.41 [0.33–0.50], p<0.001).
- The intra-patient comparison in PwHAE without current FVIII inhibitors (n=455) showed a decrease in mean ABR (95% CI) from 1.02 (0.87–1.19) to 0.54 (0.44–0.66) (rate ratio [95% CI] 0.53 [0.43–0.65], p<0.001).
- The intra-patient comparison in PwHAE with current FVIII inhibitors (n=78) showed a decrease in mean ABR (95% CI) from 5.03 (3.30–7.66) to 0.41 (0.26–0.65) (rate ratio [95% CI] 0.08 [0.04–0.15], p<0.001).

Conclusions

- This analysis describes the baseline characteristics, safety and effectiveness outcomes of Canadian PwHA treated with emicizumab before December 31, 2022; a total of 387 new PwHA were included in this analysis compared with the previous analysis (data cut-off: December 31, 2022, n=146).
- The data show that 72.8% of PwHAE had no recorded bleeds since they started emicizumab, and that there was a substantial decrease in bleeds post-emicizumab in both PwHA with and without current FVIII inhibitors.
- The safety profile of emicizumab was consistent with previous reports. The CBDR allows for a longitudinal follow-up of the Canadian HA population, which can inform healthcare practitioners and regulatory authorities of the safety and efficacy outcomes of treatments in routine clinical practice.

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While there are no longer any health authority requirements for expedited safety reporting of TE/TMAs for emicizumab, Roche understands this is an important topic for the community and will continue to monitor, assess, and report safety data for all people receiving emicizumab

References

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Disclosures

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