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POSTER ABSTRACTS

322.DISORDERS OF COAGULATION OR FIBRINOLYSIS: CLINICAL AND EPIDEMIOLOGICAL

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

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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 living with HA (PwHA) with FVIII inhibitors in 2018, and without inhibitors in 2019.
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.
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 patients with zero, traumatic, spontaneous, or joint bleeds as well as annualized bleeding rates (ABR) for any treated bleed. Intra-patient comparisons of bleeding were performed for all patients and for those with at least six months follow-up in both pre- and post-emicizumab periods as a sensitivity analysis. Effectiveness outcomes also included patients' 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.
Results: In total, 533 PwHA received at least one dose of emicizumab (PwHA $_E$) in the CBDR database. Overall, 498 (93.4%) PwHA $_E$ had severe disease, 28 (5.3%) had moderate disease, and 7 (1.3%) had mild disease. At start of emicizumab exposure, 220 (41.3%) PwHA $_E$ were <18 years old; 78 (14.6%) PwHA $_E$ had current FVIII inhibitors, 82 (15.4%) had a history of FVIII inhibitors, and 373 (70%) had no history of inhibitors (**Table 1**).
A total of 13 adverse events were reported in the entire observation period, including one event of thrombosis (occurring in one person with COVID-19), seven allergic reactions, two FVIII Inhibitor development, two neurological events (headache; and headache, nausea, and vomiting) and one case of large hematoma developed at operative site following removal of port-a-cath. Moreover, nine COVID-19 cases were reported as adverse events.
Over a median (first quartile, third quartile) follow-up time of 249 (136, 395) days, 388 (72.8%) PwHA $_E$ had no recorded bleeds. Out of 145 PwHA $_E$ with recorded bleeds, 106 had joint bleeds, 87 had traumatic bleeds, 69 had spontaneous bleeds and 46 had other bleeds **(Table 2)**.
An intra-patient comparison in all PwHA $_E$ (n=533) showed a decrease in mean (95% confidence interval [CI]) annualized bleeding rate (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-value <0.001). The Intra-patient comparison in PwHA $_E$ without current inhibitor (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-value <0.001). The Intra-patient comparison in PwHA $_E$ with current inhibitor (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-value <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 patients were included in this analysis compared to the previous one (data cut: December 31, 2021, n=146). The data shows that 72.8% PwHA $_{E}$ 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 inhibitor. The safety profile of emicizumab was consistent with previous reports. The CBDR allows for a longitudinal follow-up of the Canadian hemophilia A 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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Table 1. Demographic characteristics (baseline), disease severity, inhibitor status, treatments of people with hemophilia A enrolled in the Canadian Bleeding Disorders Registry who received emicizumab at least once prior to December 31, 2022

	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 Hx	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 (FVIII < 0.01 IU/mL), moderate (0.01 ≤ FVIII ≤ 0.05 IU/mL) and mild (0.05 < FVIII ≤ 0.40 IU/mL)
[§]Current (inhibitor at the time of receipt of the first dose of emicizumab), low titer (< 5 BU), high titer (>= 5 BU), Hx of FVIII inhibitor (inhibitor detected prior to emicizumab but no current inhibitor), no inhibitor (detected or observed yet)
BMI, body mass index; F, factor; ITI, immune tolerance induction; SD, standard deviation; Q1, first quartile; Q3: third quartile.

Table 2. Effectiveness outcomes in people with hemophilia A enrolled in the Canadian Bleeding Disorders Registry who received emicizumab at least once prior to December 31, 2022

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[$], median (IQR), n All PwHA	0.0 (0.0, 0.4), 533	0.0 (0.0, 0.4), 498	0.0 (0.0, 0.5), 28	0.0 (0.0, 0.0), 7	0.0 (0.0, 0.5), 78	0.0 (0.0, 0.0), 82	0.0 (0.0, 0.7), 373
Follow-up days for all PwHA, median (IQR), n	249 (136, 395), 533	248 (141, 393), 498	246 (67, 682), 28	681 (264, 906), 7	1067 (408, 1268), 78	238 (129, 396), 82	221 (128, 312), 373
ABR[$], median (IQR), 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 (IQR), 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[T] 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[T], 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[T], 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[T], 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 (FVIII < 0.01 IU/mL), moderate (0.01 ≤ FVIII ≤ 0.05 IU/mL) and mild (0.05 < FVIII ≤ 0.40 IU/mL)
[*]Current (inhibitor at the time of receipt of the first dose of emicizumab), Hx of FVIII inhibitor (inhibitor detected prior to emicizumab but no current inhibitor), no inhibitor (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.
[T]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; HJHS, Hemophilia Joint Health Score; PROBE, Patient Reported Outcomes Burdens and Experiences; PwHA, people with hemophilia A; SD, standard deviation; Q1, first quartile; Q3: third quartile; VAS, visual analog scale.

Figure 1