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Short Communication

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Emicizumab in Severe Hemophilia A: Clinical and Patient Determinants of Transition Within a Standardized Program

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Abstract

Background: Emicizumab (Hemlibra) became more accessible for Canadians in 2021, when Canadian Blood Services approved it under formulary for prophylaxis in patients with severe hemophilia A (PWHA) without inhibitors. This offered an alternative to factor VIII (FVIII) prophylaxis. Starting in November 2021, a coordinated effort to offer and support the transition to emicizumab was initiated for all eligible adult PWHA living in British Columbia (BC) and Yukon Territory. Of the 69 PWHA who transitioned to emicizumab, it was observed that some were early adopters whereas others demonstrated more caution and transitioned later. Our aim was to better understand patient and clinical practice factors associated with the early and late transition to emicizumab.

Methods: Retrospective data were assessed from clinical records, transition documents and available pre-transition patient-reported surveys for both patient and clinical factors.

Results: Of the 83 patients with PWHA eligible for transition, 69 transitioned to emicizumab between November 2021 and December 2023. Median time to emicizumab transition was 10 months. Younger PWHA and those with fewer cumulative comorbidities tended to delay transition to emicizumab. Geographic distance from Vancouver was not significantly associated with transition timing. In multivariable analysis, younger age remained independently associated with longer time to transition (P = 0.0008), while having five or more joints affected by hemophilic arthropathy was associated with later transition (P = 0.007).

Conclusions: Using a standardized transition program offered an opportunity to gain a deeper understanding of patient and clinical factors associated with transition to a novel agent. This analysis highlights that certain clinical factors may influence uptake of new therapies within hemophilia care and the importance of early identification of barriers to facilitate treatment uptake.

Keywords: Hemophilia A; Emicizumab; Patient-reported outcomes; Transition of care; Non-factor therapy; Health equity; Subcutaneous prophylaxis; Bispecific antibody

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Introduction

Hemophilia A is the clinical syndrome associated with a congenital deficit of factor VIII (FVIII), resulting in protracted and excessive bleeding. Severe hemophilia is defined by a FVIII level of less than 1% [1]. In this population, bleeding can occur in soft tissues, muscles, and joints, with both short- and long-term complications, including acute pain, hemophilic arthropathy, and chronic disability [2-4].

Historically, hemophilia A has been treated with either prophylactic or on-demand intravenous (IV) FVIII concentrate infusions [5]. In November 2021, emicizumab became available outside of Quebec as a publicly funded prophylactic option for patients with severe hemophilia A (PWHA) without inhibitors [6]. Emicizumab is a bispecific monoclonal antibody that mimics endogenous FVIII by co-localizing factor IXa and factor X, thereby promoting propagation of the coagulation cascade [7]. Unlike FVIII, emicizumab is administered subcutaneously and offers a reduced treatment burden compared to frequent IV infusions.

Given the large geography of British Columbia (BC) and Yukon, the potential for inequity in access to specialized care between urban and rural populations was a key consideration. In November 2021, a coordinated effort to offer and support transition to emicizumab for all eligible PWHA followed by the Adult Bleeding Disorders Program of BC/Yukon was initiated. The overarching goals were to decrease bleeding episodes, reduce treatment burden, improve function where possible, and promote autonomy.

Anecdotally, a few PWHA were early adopters and transitioned to emicizumab shortly after it became available, while others exercised more caution and transitioned months later.

The decision to transition to a novel therapy is influenced by a complex interplay of clinical status, personal beliefs, and prior illness experience [8]. Through this retrospective review, we sought to explore clinical and patient factors that may have influenced the timing of transition to emicizumab as the first publicly funded non-factor prophylaxis available to this population in Canada outside of clinical trials.

Materials and Methods

A standardized transition process was developed. The clinical team reviewed a list of patients with baseline FVIII < 1% to identify those eligible for emicizumab. Nurse practitioners provided verbal and written information, including standardized education modules (Supplementary Material 1, jh.elmerpub.com), to ensure awareness and support informed decision-making. This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. This study was approved by the Research Ethics Board (REB) at the University of British Columbia (H24-03387).

Due to limited initial national supply and clinic resources, a strategy to offer the therapy to those deemed of highest need - based on provider assessment - was implemented. Patients facing multiple challenges with maintaining high-intensity prophylaxis, high bleeding rates, or other barriers to IV administration (e.g., mental health issues, long-term care placement, disabilities) were identified. Nine such individuals were offered the opportunity to transition within the first 4 months (November 2021 to March 2022).

In January 2022, all eligible patients were offered transition. In some cases, transition was deferred to allow for depletion of home FVIII supply. Injection training was provided in-person or virtually for the first (loading dose) and fifth (maintenance dosing) injections. Peri-transition, and Patient-Reported Outcomes, Burdens and Experiences (PROBE) surveys were distributed at 0, 3, and 6 months.

Information was retrospectively collected from routinely collected clinical records, the Inherited Coagulopathy and Hemoglobinopathy Information Portal (iCHIP) [9], transition documentation, and PROBE surveys. Data from January 2018 to December 2023 were included [10-12]. PROBE surveys are scored from 0 to 1, where the higher values indicate better health status [12]. The importance of integrating patient-reported outcomes into hemophilia care has been well-characterized and is standard practice in this program.

Patient variables of interest included demographics such as age as of November 1, 2021; distance > 2 h by car from the Vancouver Adult Bleeding Disorders Program, marital or partnered status, disease burden (number of joints affected by hemophilic arthropathy), recent bleeds (clinical bleeds reported in past 2 weeks), presence of target joints, whether hemophilia was listed in their "top three health problems", treatment factors (number of factor products used since 2018, adverse events with FVIII), and comorbidities (human immunodeficiency virus (HIV), hepatitis C virus (HCV), pain, cardiovascular disease, joint surgery). Care-related factors included time since last annual review, whether emicizumab was discussed at that review, and transition setting (virtual vs. in-person). Covariates were pre-specified by the clinical team as variables of interest or secondary variables based on clinical judgment. Only variables of interest were entered into the multivariable model; secondary covariates were collected and examined only in univariate analyses.

Proportions were calculated for categorical variables and medians with interquartile ranges (IQRs) for continuous variables due to skewed distributions. Differences between early (transition ≤ 9 months after availability) and late (transition ≥ 10 months) groups were evaluated using Chi-square or Fisher's exact test for categorical variables and Wilcoxon rank-sum for continuous variables. The time frames for the categorization of early and late transitioning PWHA were determined by splitting the median values of the transition times available.

Univariate and multivariable linear regression analyses were used to evaluate associations between independent variables and time to transition (in months). Variables of interest with $P < 0.10$ in univariate analysis were entered into the multivariable model. Regression coefficients, 95% confidence intervals, and P values were reported. Model fit was assessed using residual analysis and analysis of variance (ANOVA).

Results

Of the 83 PWHA eligible for transition, 69 (83%) transitioned to emicizumab between November 2021 and December 2023. Among the initial nine patients prioritized for early transition, three transitioned within the first 4 months, and only one transitioned within the first 2 months. Characteristics of the transitioned population are outlined in Table 1. The median time to emicizumab transition was 10 months (range 0 - 21, IQR 25th - 75th: 7; 13), as outlined in Table 2.

The median time to transition was 10 months (IQR 7 - 13). Among the 69 transitioned patients, the median age was 31 years, and 36% lived more than 2 h from Vancouver.

On univariate analysis, a longer time to transition was associated with younger age ($P < 0.001$), longer time since last annual review ($P = 0.083$), absence of HIV ($P = 0.012$) or HCV ($P = 0.003$), not listing hemophilia among their "top three health problems" ($P = 0.009$), lower number of target joints ($P = 0.011$), and absence of cardiovascular risk factors ($P = 0.008$) (Supplementary Materials 2, 3, jh.elmerpub.com).

In multivariable analysis, younger age remained independently associated with longer time to transition ($P = 0.0008$), as did having five or more joints affected by hemophilic arthropathy ($P = 0.007$). There was no significant difference for those with two to four joints compared to those with zero to one joint affected ($P = 0.81$). The model was statistically significant (ANOVA $P = 0.007$), with an adjusted R^2 of 0.224, indicating that it explained 22.4% of the variability in transition timing. Each additional year of age was associated with a 0.15-month shorter time to transition (age centered at 31 years), as demon-

Table 1. Characteristics of the Transitioned Population of PWHA Included in the Standardized Transition to Emicizumab at the Adult Bleeding Disorders Program of British Columbia/Yukon

Characteristic	All (n = 69)
Age (years) at time of drug availability, median (IQR)	31 (26, 40)
> 2 h by car from Vancouver, n (%)	25 (36.2)
Hemophilic arthropathy (6 joints involved), n (%)	
0 - 1 joints	36 (52.2)
2 - 4 joints	29 (42.0)
5 or more joints affected	4 (5.8)
HIV, n (%)	10 (14.5)
HCV (chronic diagnosis), n (%)	23 (34.3)
If HCV - cleared, n (%)	21 (95.5)
Filled out EQ5D/PROBE survey, n (%)	52 (75.4)
Composite EQ5D, median (IQR)	0.854 (0.714, 0.942)
Composite PROBE score, median (IQR)	0.791 (0.650, 0.907)

PWHA: patients with severe hemophilia A; PROBE: Patient-Reported Outcomes, Burdens and Experiences; IQR: interquartile range; HIV: human immunodeficiency virus; HCV: hepatitis C virus.

strated in Table 3.

As of December 2023, four patients transitioned back to FVIII prophylaxis: one due to development of inhibitory anti-drug antibodies against emicizumab, one due to cutaneous reaction, and two due to perceived insufficient hemostasis. Time to discontinuation ranged from 1 week to 7 months.

Reasons cited for declining transition included the following: individuals on daily prophylaxis with a very active lifestyle (n = 1), on daily prophylaxis but not active (n = 1), patients unwilling to change now but open to future transition (n = 5), never interested (n = 4), only in the country briefly and sourcing their own factor (n = 2) and declined for unknown reasons (n = 1).

Discussion

To our knowledge, this is the first study to statistically examine accessibility and comorbidity burden as associations with emicizumab uptake timing. Despite their therapeutic promise, uptake of novel treatments in hemophilia has been slower than expected, reflecting concerns over long-term safety, durabil-

Table 2. Median Time to Emicizumab Transition in the Standardized Transition Program at the Adult Bleeding Disorders Program of British Columbia/Yukon

Transition time (months)	N	Minimum	Maximum	Median	IQR 25%	IQR 75%
Early	28	0	9	7	4.5	8
Late	41	10	21	12	11	14
All	69	0	21	10	7	13

IQR: interquartile range.

Table 3. Regression Coefficients (95% CI) for the Outcome, Months to Transition From When Emicizumab Was Available

Variable	Regression coefficient	95% confidence limits	P value
Intercept	10.59	8.87, 12.31	< 0.0001
Age (years) at time of emicizumab availability	-0.15	-0.23, -0.06	0.0008
> 2 h by car from Vancouver	0.75	-1.43, 2.92	0.50
Hemophilic arthropathy (reference: 0 - 1 joints)			
2 - 4 joints affected	-0.26	-2.45, 1.94	0.81
5 or more joints affected	6.50	1.84, 11.16	0.007
History of adverse events on a previous factor concentrate	-5.52	-11.94, 0.90	0.09

CI: confidence interval.

ity, cost, reimbursement challenges, and patient selection [13]. In this cohort, younger PWHA and those with fewer cumulative comorbidities tended to delay transition to emicizumab. In contrast, older patients without joint disease or comorbid burden transitioned sooner. This suggests that individuals with longer disease duration or lived experience of complications were more inclined to try a novel agent.

Several factors may underlie the pattern that was observed in this cohort. Older patients may have had more direct experience with the physical and emotional burden of long-term IV prophylaxis, increasing their motivation to trial a novel agent. Longer-standing relationships with the clinic may also have fostered greater trust in provider recommendations. Additionally, patients more engaged with care may have been more familiar with the development of emicizumab and anticipated its availability.

Interestingly, the initial group offered early transition - despite being clinically prioritized - did not show a marked early uptake, highlighting the multifactorial nature of therapeutic decision-making. Clinical need alone does not necessarily translate into rapid adoption. Patient autonomy, readiness, and personal risk-benefit considerations likely played significant roles. These concepts are likely to be better understood through future research that addresses the multifactorial determinants influencing the adoption of novel therapies during care transitions.

Geographic distance from Vancouver was not significantly associated with transition timing. This may reflect the use of virtual care pathways and hybrid education models, ensuring patients from remote areas had access comparable to those in urban centers. The lack of difference between in-person and virtual transition pathways supports the role of telemedicine in facilitating access to novel therapies in rare disease populations. This finding is in keeping with previous work that demonstrates the role for tele-consenting and remote initiation models for timely treatment start in hematologic care, establishing telehealth as a viable pathway for integrating novel therapies across varied patient settings [14].

The attrition rate from emicizumab was low (four of 69, or 5.8%), with reasons consistent with known complications. These findings suggest that, overall, the transition was successful and durable.

This study included only patients who transitioned to emicizumab during the study period; individuals who did not transition were not assessed. Accordingly, the findings are susceptible to treatment-selection bias and may not generalize to all eligible patients. Future studies that include those who did not transition to novel therapies would supplement this work and assist in generalizability.

With several novel hemophilia therapies on the horizon - including next-generation FVIII agents, bispecific mimetics like Mim8, rebalancing agents such as tissue factor pathway inhibitor (TFPI) antibodies (concizumab, marstacimab) and antithrombin siRNA therapeutic (fitusiran) approach - understanding what influences patient uptake is increasingly important [8]. Previous work addressing the integration of novel hemophilia therapies has highlighted the need to adapt care delivery models - alongside reimbursement frameworks - to fit diverse healthcare system capacities [15]. Structured transition programs like this one provide an opportunity to explore patient preferences and values and to align therapeutic plans with long-term goals.

Supplementary Material

Suppl 1. Standardized education model for patient transition to emicizumab.

Suppl 2. Patient demographics and variables of interest.

Suppl 3. Secondary variables in study population (secondary variables were not included in the multivariable analysis).

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Conflict of Interest

The authors declare that they have no conflict of interest concerning this article.

Informed Consent

Not applicable.

Author Contributions

SJ designed the research, IBH collected and analyzed the data. IBH, MB and SJ contributed to the manuscript, and SJ approved the final submission.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

FVIII: factor VIII; IV: intravenous; PWHA: patients with severe hemophilia A; REB: Research Ethics Board; PROBE: Patient-Reported Outcomes, Burdens and Experiences; iCHIP: Inherited Coagulopathy and Hemoglobinopathy Information

Portal; IQR: interquartile range; HIV: human immunodeficiency virus; HCV: hepatitis C virus

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