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ORIGINAL ARTICLE

The impact of extended half-life factor concentrates on patient reported health outcome measures in persons with hemophilia A and hemophilia B

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Abstract

Background: Recombinant factors VIII and IX Fc (rFVIIIFc/rFIXFc) were the only available extended half-life (EHL) products in Canada during 2016 to 2018.

Objectives: To evaluate if patient-reported outcome measures (PROMs) improved in Canadian persons with hemophilia who switched from standard half-life (SHL) to EHL products (rFVIIIFc/rFIXFc).

Patients/Methods: This prospective cohort study enrolled persons with moderate or severe hemophilia aged ≥6 years who switched to rFVIIIFc/rFIXFc (2016-2018) and those who remained on SHL. Health-related quality of life (HRQoL) was assessed using the Haemophilia-specific Quality of Life (Haem-A-QoL) and 36-item Short-Form Survey (SF-36) at baseline, 3-months, 12 months, and 24 months. Other PROMs included the Work Productivity and Impairment Questionnaire, chronic pain scale, partner/parent ratings of mood, International Physical Activity Questionnaire,

and Treatment Satisfaction Questionnaire for Medication. We identified meaningful changes using minimally important difference for SF-36 and responder definition for Haem-A-QoL.

Results: We enrolled 25 switchers (16 rFVIIIFc, 9 rFIXFc) and 33 nonswitchers. Those switched to rFVIIIFc/rFIXFc had improved overall HRQoL, and improved subscale physical activity, mental health, and social functioning at 3 months. The rFIXFc switchers had improved chronic pain and ability to engage in normal activities while the rFVIIIFc switchers had improved treatment satisfaction. There was no change in work impairment after the switch. Observed improvement disappeared by 24 months in most domains.

Conclusion: Switching from SHL to rFVIIIFc/rFIXFc resulted in short-term meaningful improvement in overall HRQoL and other PROMs in a small proportion. Longitudinal changes on PROMs are affected by ceiling effects and response shift, warranting further studies in instrument optimization in the era of EHL and nonfactor products.

KEYWORDS
extended half-life, hemophilia A, hemophilia B, patient-reported outcomes, quality of life

Essentials

- It is unclear how switches from standard to extended half-life factor affect patient-reported outcomes.
- A multicenter prospective cohort study of patients who switched to recombinant Factor VIII/IX Fc was conducted.
- The switch improved health-related quality of life and physical, mental, and social functioning in some patients.
- Responsiveness of current tools and ceiling effects limit the perceived impact of novel therapy.

1 | INTRODUCTION

In persons with hemophilia and a severe bleeding phenotype, prophylaxis with factor or nonfactor products is the current standard of care for preventing recurrent or life-threatening bleeds and to maintain long-term joint health.[1] Prophylaxis with standard half-life (SHL) factor concentrates usually requires frequent infusions for optimal bleed prevention, which may adversely affect quality of life and contribute to variable treatment adherence. Extended half-life (EHL) factor concentrates have the advantages of either reducing the frequency of prophylactic infusions, thereby reducing the treatment burden, or achieving higher factor trough levels,[1] which may improve health outcomes. Recombinant factor VIII and factorIX Fc fusion proteins (rFVIIIFc, rFIXFc) were the first and only available EHL products available to persons with hemophilia in Canada during the period January 2016 to April 2018. The impact of switching to EHL factor concentrates on patient- and caregiver-reported outcome measures (PROMs) is unclear. In this Canadian prospective cohort study, we evaluated the changes in a comprehensive battery of PROMs in pediatric and adult males who switched to rFVIIIFc (antihemophilic factor [recombinant] Fc fusion protein; Eloctate/Elocta, Sanofi) and rFIXFc (coagulation factor IX [recombinant] Fc fusion protein; Alprolix, Sanofi) over a 24-month period, compared to changes in those who remained on SHL factor concentrates. We hypothesized that switching from SHL to EHL factor concentrates would not only lead to improvement in overall health-related quality of life (HRQoL), but also improvements in other domains such as physical function and activities, chronic pain, mental health, work/school participation, and treatment satisfaction. We have previously reported on the impact of switching to rFVIIIFc/rFIXFc on provider measured outcomes, which showed a reduction in prophylactic FVIII/FIX infusion frequency and a statistically significant reduction in annualized FIX usage.[2] Annualized bleeding rates dropped significantly in children who switched to rFVIIIFc, and remained stable in adults who switched to rFVIIIFc or rFIXFc.[2] Here, we report on PROMs and compare them with other relevant published observations.

2 | METHODS

In this prospective cohort study, all consecutive patients aged ≥6 years with moderate (FVIII/FIX 1–5 IU/dL) and severe (<1 IU/dL) hemophilia A and B without active inhibitors attending eight major Canadian hemophilia centers were screened during routine visits between April 2016 and June 2018. Patients were excluded if they were unable to provide informed consent, had another bleeding disorder, had hypersensitivity/severe allergic reactions to factor concentrates, or were participating in a trial with another factor

concentrate. Eligible participants were enrolled during the time period when rFVIIIFc/rFIXFc became available in Canada, regardless of their treatment regimen (prophylaxis or on-demand, SHL or EHL factor concentrates). Hemophilia treaters made the decision to switch a patient to an EHL factor concentrate or maintain on SHL, based on clinical judgment and/or shared decision making, regardless of study participation. The most common reasons for switches to rFVIIIFc/rFIXFc in a Canadian cohort have been described,[2] including infusion frequency/treatment burden, quality of life, and patient/family preferences. PROMs were collected at baseline, 3-months ± 2 weeks, 12 ± 2 months, and 24 ± 2 months using paper-based questionnaires. The 3-month PROM time point was added to routine annual clinic visits, as we anticipated a higher likelihood of detecting meaningful changes at 3 months compared with 12 months due to response shift, representing changes in self-reported quality-of-life due to shifts in internal standards and expectations.[3] The study was approved by the institutional research ethics boards.

2.1 | Patient-relevant PROMs

We selected age-appropriate PROMs based on validity, relevance, and burden of administration. A standard set of 10 patient-relevant health outcomes was recently developed by an international working group to harmonize longitudinal data collection and improve value-based health care for persons with hemophilia.[4] The panel also recommended suitable outcome measure instruments based on psychometric properties. We present our PROM instruments using the framework proposed by the International Standard Outcomes Set working group (Table 1).[4]

Overall HRQoL was assessed using both generic and hemophilia-specific instruments. Adult and pediatric patients (or their caregivers) completed the 36-Item Short-Form Health Survey (SF-36). This generic HRQoL instrument offers advantages of population norm-based scoring, subscale scores, and indirect comparison with other chronic diseases.[5] It consists of 36 questions in eight domains (over the preceding 4 weeks), with scores ranging from 0 to 100 (100 representing the best HRQoL). Two summary scores, Physical Component Summary (PCS) and Mental Component Summary (MSC), are derived from the individual domains and reported using population normal based scoring.

We selected the Haemophilia-specific Quality of Life (Haem-A-QoL) as the disease-specific HRQoL instrument for adult patients. This 46-item HRQoL instrument spans 10 domains, with a transformed score on a scale from 0 to 100 (100 signifying the worst HRQoL).[6] The instrument demonstrated good psychometric properties including reliability and convergent validity with SF-36 in adults with hemophilia,[7] as well as sensitivity to change over time in clinical trials.[8,9] The Canadian Hemophilia Outcomes Kids Life Assessment Tool (CHO-KLAT) version 2.0 was planned as the disease-specific HRQoL instrument for pediatric patients. However, as fewer than five pediatric participants (<18 years) had paired results, we elected to not analyze the data due to small numbers.

The Work Productivity and Impairment Questionnaire plus Classroom Impairment Questionnaire: Hemophilia Specific (WPAI+CIQ:HS) is a nine-item questionnaire designed to quantify the extent of work or school absenteeism, loss of work/school productivity, and activity impairment within the preceding 7 days.[10,11] The results are presented as impairment percentages, with 100% representing the greatest impairment related to hemophilia. The International Physical Activity Questionnaire (IPAQ), 7-item version, is used to assess physical activity in the prior week across multiple domains including leisure, domestic activities, and work- and transport-related activity.[12,13] Metabolic equivalents of task (MET)-minutes per week can be calculated from the amount of time spent in mild, moderate, and vigorous activities. The abbreviated nine-item Treatment Satisfaction Questionnaire for Medication (TSQM-9) measures patient satisfaction with medications within the preceding 2 to 3 weeks.[14] It provides scores on the effectiveness, convenience, and global satisfaction domains, where a higher score indicates better treatment satisfaction. The chronic pain numeric rating scale (NRS) or visual analog scale (VAS) assesses the intensity of pain associated with hemophilia in the preceding 4 weeks, on a Likert scale from 0 to 10, 10 being the worst pain. Similarly, we asked the partners or parents to rate the participants' mood at baseline and 3 months on a Likert scale of 0 to 10, 10 representing the best mood. We developed a simple questionnaire consisting of 2 questions at 24-month follow-up to assess patient preference for SHL or EHL concentrates. Participants were asked in retrospect if they would have changed their initial choice (SHL or EHL products) if they had the option and, if so, why.

2.2 | Statistical analysis

Baseline demographic, clinical characteristics, and PROM data were summarized using descriptive statistics. Mean (standard deviation [SD]) or median and interquartile range were reported for continuous variables, whereas frequency counts and percentage were reported for categorical variables. Analyses were performed, stratified by treatment group (switchers to rFVIIIFc/rFIXFc and those who remained on SHL). Comparisons are focused on within-individual changes preswitch versus 3 months and 24 months after switching to EHL, among those with paired results. No direct comparisons were performed between switchers to rFVIIIFc/rFIXFc and those who remained on SHL-FVIII/FIX, due to differences in baseline characteristics. Only results from PROM instruments with five or more respondents were reported.

Testing for statistical significance was not performed due to small numbers. To assess for clinically meaningful changes, we used the minimally important difference (MID) threshold for SF-36 and the responder definition for Haem-A-QoL total score and relevant subscales. Previously reported responder definitions for Haem-A-QoL were "Physical Health" (−10), "Sports and Leisure" (−10), total score (−7).[15] The previously reported MID thresholds for SF-36 were PCS (2-3), MCS (3), physical functioning (2-3), role physical

TABLE 1 List of patient reported outcome measures (PROMs) for patient relevant core health outcomes in hemophilia used in our study, using the framework proposed by the International Standard Outcomes Set working group[4]

Outcome dimension	Our study (adults)	Our study (pediatrics)	International Standard Outcomes Set recommendations
Ability to engage in normal daily activities	Haem-A-QoL Physical Health, Sports & Leisure subscales	–	– HAL and pedHAL (use of transportation, self-care, household tasks) – FISH[a] (lower-income countries)
Number of days lost	WPAI+CIQ:HS	–	– Number days absent – FTEs worked or in school
Chronic pain	– Chronic pain NRS – SF-36 Bodily Pain subscale	– Chronic pain VAS – SF-36 Bodily Pain subscale	PROBE (chronic pain)
Physical functioning	– SF-36 Physical Functioning subscale – IPAQ	– SF-36 Physical Functioning subscale	HAL, pedHAL
Social functioning	– Haem-A-QoL Partnership, Family Planning subscales		– Haemo-QoL-A (role functioning impact subscale) – CHO-KLAT
Mental health	– SF-36 Mental Health subscale – Partner/parent ratings of mood	– SF-36 Mental Health subscale – Partner/parent ratings of mood	– Haemo-QoL-A (emotional impact subscale) – CHO-KLAT
Treatment burden[a]	– Haem-A-QoL Treatment subscale – TSQM-9		
Patient preference[a]	– Question on preference for SHL or EHL		

Abbreviations: CHO-KLAT, the Canadian Hemophilia Outcomes–Kids Life Assessment Tool; EHL, extended half-life; FISH, Functional Independence Score in Haemophilia; FTE, full time equivalents; Haem-A-QoL, Haemophilia-specific Quality-of-Life questionnaire; HAL, Haemophilia Activity List; HRQoL, health-related quality of life; IPAQ, International Physical Activity Questionnaire; NRS, numeric rating scale; PROBE, Patient Reported Outcomes, Burdens and Experiences; SF-36, 36-Item Short-Form Health Survey; SHL, standard half-life; TSQM-9, Treatment Satisfaction Questionnaire for Medication; VAS, visual analog scale; WPAI+CIQ:HS, Work Productivity and Impairment Questionnaire.

[a]Treatment burden and patient preference are not among the list of core health outcomes identified by the international working group, but included in our study.

functioning (2), bodily pain (2-3), general health perception (2-3), vitality (2-3), social functioning (3), role emotional functioning (4), and mental health (3).[16] We reported the SF-36 PCS and MCS using the Canadian population norm-based scoring, centering the Canadian population mean to 50 and the SD to 10.[17] For PROMs with no established MIDs, we estimated the threshold for meaningful changes as half of a SD.[18] R statistical software (R Foundation for Statistical Computing, Vienna, Austria) was used for analysis.

3 | RESULTS

We enrolled 58 patients, 25 who switched to EHL factor concentrates (rFVIIIFc, n = 16; rFIXFc, n = 9) and 33 who remained on SHL-FVIII/FIX (Table 2). Most switchers (84%) were adults aged ≥18 years. Compared to patients who remained on SHL, those who switched to EHL concentrates were older, had a trend toward higher median Hemophilia Joint Health Score score, and had higher annualized bleeding rates (ABRs) in the 12-month period prior to enrollment (Table 2).

3.1 | Overall HRQoL

Participants who switched to rFIXFc achieved a mean reduction (indicating improvement) in the Haem-A-QoL total score of −5.0 (SD, 7.4) at 3-months, with 2/7 (29%) achieving a clinically meaningful reduction based on pre-specified responder definition (Table 3). Switchers to rFVIIIFc experienced a smaller magnitude of reduction in the total score (mean, −2.3; SD, 8.5) at 3 months, with only 3 of 25 (12%) achieving the prespecified responder definition (Table 4). The change in the direction of improvement disappeared by 24 months for both groups. Among patients who remained on SHL products, the total Haem-A-QoL score remained unchanged in SHL-FVIII and reduced by a mean of −4.6 at 3 months in SHL-FIX (not shown).

Approximately half of switchers to rFIXFc and switchers to rFVIIIFc achieved a meaningful improvement (based on the MID) in SF-36 PCS and MCS, respectively (Table 5). The SF-36 radar plots demonstrated improvements in selected SF-36 domains in patients who switched to rFIXFc, not notable in those who switched to rFVIIIFc (Supporting Information).

TABLE 2 Baseline characteristics in patients who switched to recombinant factor VIII and IX Fc (rFVIIIFc, rFIXFc) and those who remained on standard half-life factor concentrates

	Switcher to rFVIIIFc (N = 16)	Switcher to rFIXFc (N = 9)	Nonswitcher: rFVIII (N = 27)	Nonswitcher: rFIX (N = 6)
Age, median (IQR)	41 (34-51)	43 (33-55)	26 (19-37)	22 (15-27)
Pediatric (<18 y), n (%)	3 (19)	1 (11)	6 (22)	2 (33)
Severe hemophilia, n (%)	13 (81)	5 (56)	21 (78)	4 (67)
Prophylaxis, n (%)	16 (100)	7 (78)	24 (89)	4 (67)
Median HJHS score (IQR)	28 (13-48), n = 12 available	17 (5-28), n = 4 available	8 (4-16), n = 15 available	3 (2-4), n = 5 available
No. patients with target joints baseline (%)	2 (13)	3 (33)	2 (7)	1 (17)
HIV infection, n (%)	10 (63)	1 (11)	1 (4)	0
Active HCV infection, n (%)	1 (6)	0	1 (4)	0
Baseline ABRs in 12-month period prestudy, median (IQR)	3.0 (1.0-10.5)	3.0 (1.0-8.0)	0 (0-1.0)	2.0 (1.0-2.0)
Baseline Haem-A-QoL total score, mean (SD)	44.4 (13.5)	53.0 (8.3)	37.4 (10.0)	33.2 (5.7)
Baseline SF-36 PCS (norm-referenced), mean (SD)	41.3 (10.7)	38.9 (5.1)	46.6 (8.9)	42.9 (15.3)
Baseline SF-36 MCS (norm-referenced), mean (SD)	47.1 (11.9)	41.7 (12.6)	52.5 (10.8)	53.9 (4.3)

Abbreviations: ABRs, annualized bleeding rates; Haem-A-QoL, Haemophilia-specific Quality of Life questionnaire; HCV, hepatitis C virus; HJHS, Hemophilia Joint Health Score; IQR, interquartile range; MCS, Mental Component Summary; PCS, Physical Component Summary; rFIX, recombinant factor IX; rFVIII, recombinant factor VIII; SD, standard deviation; SF-36, 36-Item Short-Form Health Survey.

3.2 | Daily activities

Haem-A-QoL Physical Health and Sports & Leisure domains were used as surrogates for participants' ability to engage in normal activities. We observed meaningful improvements based on the prespecified responder definitions in these domains in the rFIXFc but not rFVIIIFc group. Switchers to rFIXFc experienced a mean reduction −12.9 at 3 months and −6.3 at 24 months in the Physical Health domain and a mean reduction of −3.3 at 3 months and −4.6 at 24 months in the Sports and Leisure domain (Table 3). Correspondingly, 71% (5/7) and 29% (2/7) individuals met the prespecified responder definition threshold in Physical Health and Sports and Leisure domains at 3 months, respectively.

3.3 | Work productivity

Among participants who completed work/school productivity questionnaires, 6 of 9 (67%) on rFIXFc and 10 of 14 (71%) on rFVIIIFc were either employed or attending school. The overall work/classroom impairment due to hemophilia was low among switchers to rFIXFc (mean 24% at baseline, 30% at 3 months, 20% at 24 months) and switchers to rFVIIIFc (10% baseline, 27% at 3 months, 11% at 24 months). Among those with paired pre- and postswitch results, 1 of 5 (20%) switchers to rFIXFc and 3 of 8 (38%) switchers to rFVIIIFc achieved a meaningful improvement (one-half or more of a SD) at 3 months. In comparison, most (83%-87%) patients remaining on SHL-FVIII/FIX were employed or in school, with a similarly low overall impairment throughout the study (SHL-FIX, 3%-29%; SHL-FVIII, 6%-13%). Three of 13 (23%) patients who remained on SHL-FVIII experienced an improvement over one-half of a SD at 3 months, whereas the numbers with paired results were <5 in the SHL-FIX group. The proportion of work/class time missed in the preceding 7 days due to hemophilia was negligible throughout the study (0% to 1% at most time points) in switchers and nonswitchers.

3.4 | Chronic pain

Following product switch from SHL-FIX to rFIXFc, we observed a reduction in chronic pain rating on a 0 to 10 Likert scale (from a baseline score of 5 to 2 at 3 months), concomitant with an improvement in the SF-36 Bodily Pain subscale from a baseline mean ± SD of 53.9 ± 18.5 to 66.9 ± 22.9 at 3 months and 60.8 ± 20.8 at 24 months (Supporting Information). We did not observe improvements in chronic pain in patients who switched to rFVIIIFc or those who remained on SHL-FVIII/FIX. At 3 months and 24 months, 56% of patients who switched to rFIXFc achieved the MID in the SF-36 Bodily Pain subscale, compared to 33% and 22% of patients who switched to rFVIIIFc.

3.5 | Mental health

We observed improved mood in switchers to rFIXFc but not in those who remained on SHL-FIX, as measured by both partner/parent-rated mood and the SF-36 Mental Health subscale (Supporting Information). Proxy-rated mood rating increased from a baseline mean of 5.1 ± 2.1 to 6.6 ± 2.9 at 3 months in switchers to rFIXFc, corresponding to an increase in the SF-36 Mental Health subscale from 63.3 ± 21.2 to 67.8 ± 20.5 at 3 months (56% met the MID threshold). Switchers to rFVIIIFc also experienced an improvement in the SF-36 Mental Health subscale, from a baseline mean of

TABLE 3 Changes in the Haem-A-QoL scores over time in patients who switched from SHL Factor IX (FIX) to EHL rFIX Fc

	Baseline score	Change from baseline to 3 months	Change from baseline to 12 months	Change from baseline to 24 months
Sample size	N = 8	N = 7	N = 8	N = 8
Physical Health				
Mean (SD)	53.1 (20.0)	−12.9 (14.1)	0.6 (20.6)	−6.3 (14.8)
Median (IQR)	57.5 (38.8–66.3)	−10.0 (−20.0 to −7.5)	0 (−12.5 to 16.3)	−2.5 (−13.8 to 2.5)
Feelings				
Mean (SD)	49.2 (21.0)	−15.2 (15.7)	−7.8 (28.9)	−11.7 (23.7)
Median (IQR)	53.1 (35.9–64.1)	−12.5 (−21.9 to −3.1)	−9.4 (−18.8 to 1.6)	−12.5 (−23.4 to −9.4)
Views of Yourself				
Mean (SD)	55.6 (14.5)	−2.1 (15.8)	−5.0 (13.1)	−3.8 (13.0)
Median (IQR)	55.0 (47.5–63.8)	−5.0 (−12.5 to 5.0)	−7.5 (−11.3 to 2.5)	0 (−5.0 to −15.0)
Sports and Leisure				
Mean (SD)	62.3 (16.5)	−3.3 (21.4)	−13.1 (32.8)	−4.6 (15.5)
Median (IQR)	57.5 (53.8–76.6)	0 (−17.1 to 13.8)	−5.0 (−22.8 to 7.5)	0 (−10.0 to 5.6)
Work and School				
Mean (SD)	58.3 (3.2)	0.4 (11.7)	−4.5 (13.4)	−1.3 (5.2)
Median (IQR)	56.3 (56.3–60.9)	0 (−6.3 to 2.1)	−3.1 (−15.6 to 4.7)	0 (−6.3 to 0)
Dealing With Hemophilia				
Mean (SD)	83.3 (19.4)	3.6 (8.1)	1.0 (10.4)	5.2 (14.0)
Median (IQR)	87.5 (77.1–100.0)	0 (0–8.3)	0 (−2.1 to 8.3)	0 (−2.1 to 10.4)
Treatment				
Mean (SD)	49.6 (15.8)	−2.7 (15.9)	−5.5 (16.2)	−7.4 (16.8)
Median (IQR)	46.9 (39.1–53.1)	−9.4 (−10.9 to 9.4)	−3.1 (−8.6 to 0.8)	−3.1 (−7.0 to 0.8)
Future				
Mean (SD)	51.3 (15.1)	−7.1 (9.1)	−1.9 (7.0)	−3.8 (6.9)
Median (IQR)	52.5 (46.3–61.3)	−10.0 (−12.5 to 0)	−2.5 (−6.3 to 1.3)	−5.0 (−6.3 to 1.3)
Family Planning				
Mean (SD)	23.3 (15.4)	7.6 (33.4)	7.3 (25.3)	6.3 (34.8)
Median (IQR)	25.0 (15.6–31.3)	6.3 (−9.4 to 24.0)	11.5 (−6.3 to 25.0)	0 (−12.5 to 21.9)
Partnership and Sexuality				
Mean (SD)	40.6 (33.2)	−11.1 (16.4)	−5.2 (38.3)	−1.0 (37.4)
Median (IQR)	29.2 (20.8–68.8)	−8.3 (−22.9 to 0)	−4.2 (−25.0 to 4.2)	0 (−18.8 to 18.8)
Total score				
Mean (SD)	53.0 (8.3)	−5.0 (7.4)	−4.6 (9.3)	−1.7 (12.1)
Median (IQR)	51.6 (47.7–57.2)	−3.6 (−7.2 to −0.4)	−1.8 (−10.1 to 1.1)	−0.1 (−11.1 to 6.6)

Abbreviations: Haem-A-QoL, Haemophilia-specific Quality of Life questionnaire; IQR, interquartile range; SD, standard deviation.

75.0 ± 18.1 to 78.8 ± 16.4 at 3 months (53% met the MID threshold). Initial improvements disappeared at 24 months for both rFVIIIFc and rFIXFc groups.

3.6 | Physical functioning

There was a clinically meaningful improvement (based on the pre-specified MID) in the SF-36 Physical Function subscale in patients who switched to rFIXFc (67.8 ± 19.2 to 71.7 ± 21.8) and those who switched to rFVIIIFc (71.5 ± 28.2 to 75.7 ± 24.2) at 3 months. Approximately 40% of switchers to rFIXFc and rFVIIIFc achieved the MID threshold (Table 5).

Patients who switched to rFIXFc experienced increased MET-minutes per week from baseline (3291 ± 4864) to 3 months (4676 ± 5865), also sustained at 24 months (Supporting Information). In comparison, patients who remained on SHL-FIX also experienced increased physical activity initially, but the activity level returned to baseline at 24 months. The proportion who achieved a clinically meaningful increase (over one-half of a SD) was similar between switchers to rFIXFc and nonswitchers (38% vs 40% at both 3 months and 24 months). Patients who switched

TABLE 4 Changes in Haem-A-QoL scores over time in patients who switched from SHL FVIII to EHL rFVIII Fc

	Baseline score	Change from baseline to 3 months	Change from baseline to 12 months	Change from baseline to 24-months
Sample size	*N* = 13	*N* = 12	*N* = 9	*N* = 8
Physical Health				
Mean (SD)	42.3 (23.9)	−3.3 (9.6)	−3.3 (10.3)	5.0 (17.7)
Median (IQR)	40.0 (30.0–60.0)	−2.5 (−5.0 to 0)	−5.0 (−15.0 to 5.0)	2.5 (−6.3 to 6.3)
Feelings				
Mean (SD)	25.0 (17.1)	−3.6 (12.9)	−6.3 (15.0)	−1.6 (14.5)
Median (IQR)	25.0 (18.8–31.3)	−6.3 (−7.8 to 1.6)	0 (−12.5 to 0)	0 (−7.8 to 1.6)
Views of Yourself				
Mean (SD)	50.4 (11.3)	1.7 (6.5)	2.2 (18.7)	1.9 (17.3)
Median (IQR)	55.0 (45.0–55.0)	0 (−5.0 to 5.0)	0 (−5.0 to 5)	0 (−10.0 to 5.0)
Sports and Leisure				
Mean (SD)	47.8 (17.5)	−0.4 (24.5)	−1.9 (18.1)	5.0 (21.0)
Median (IQR)	50.0 (38.8–58.3)	10.0 (−7.5 to 13.8)	2.5 (−11.3 to 6.3)	0 (−11.3 to 22.5)
Work and School				
Mean (SD)	58.1 (15.3)	0.8 (10.3)	−7.8 (16.4)	−1.3 (8.5)
Median (IQR)	56.3 (50.0–62.5)	0 (−6.3 to 3.1)	−3.1 (−12.5 to 1.6)	0 (−6.3 to 0)
Dealing With Hemophilia				
Mean (SD)	90.4 (9.5)	−7.6 (17.6)	−5.6 (11.8)	−3.1 (7.6)
Median (IQR)	91.7 (83.3–100.0)	−4.2 (−8.3 to 0)	0 (−8.3 to 0)	−8.3 (−8.3 to 2.1)
Treatment				
Mean (SD)	42.9 (14.7)	−3.0 (13.1)	−1.6 (17.7)	2.1 (19.4)
Median (IQR)	37.5 (34.4–56.3)	−1.6 (−7.8 to 2.6)	−3.1 (−9.4 to 6.3)	−3.1 (−5.2 to 14.8)
Future				
Mean (SD)	41.5 (14.8)	−1.7 (12.1)	−0.6 (5.3)	3.8 (11.9)
Median (IQR)	40.0 (30.0–50.0)	0 (−11.3 to 6.3)	0 (−5.0 to 5.0)	2.5 (−1.3 to 5)
Family Planning				
Mean (SD)	25.0 (38.7)	−14.8 (35.7)	−5.0 (27.4)	3.1 (6.3)
Median (IQR)	0 (0–25.0)	0 (−6.3 to 0)	0 (0)	0 (0–3.1)
Partnership and Sexuality				
Mean (SD)	21.8 (32.5)	2.1 (14.7)	−5.2 (13.3)	−8.3 (13.4)
Median (IQR)	8.3 (0–33.3)	0 (0 to 8.3)	0 (−4.2 to 0)	0 (−12.5 to 0)
Total score				
Mean (SD)	44.4 (13.5)	−2.3 (8.5)	−6.1 (9.7)	−0.5 (10.0)
Median (IQR)	39.9 (36.2–51.2)	−0.1 (−6 to 1.6)	−6.8 (−11.7 to 2.4)	−1.6 (−6.6 to 6.0)

Abbreviations: Haem-A-QoL, Haemophilia-specific Quality of Life questionnaire; SD, standard deviation.

to rFVIIIFc demonstrated an initial increase in the MET-minutes per week from baseline (3099 ± 3474) to 3 months (5241 ± 5162), which was not seen in nonswitchers. More switchers experienced a clinically meaningful increase at 3 months compared to nonswitchers.

3.7 | Social functioning

Patients who switched to rFVIIIFc and rFIXFc experienced a meaningful improvement in the SF-36 Social Functioning subscale. Among switchers to rFIXFc, 4 (44%) and 3 (33%) patients achieved an MID in the Social Functioning subscale at 3 months and 24 months, respectively. Likewise, 7 (47%) and 4 (44%) switchers to rFVIIIFc achieved an MID at 3 months and 24 months (Table 5).

There was no consistent pattern in the changes in the Haem-A-QoL Partnership and Sexuality and Family Planning subscales following switching to rFVIIIFc/rFIXFc (Tables 3 and 4). Switchers to rFIXFc, but not switchers to rFVIIIFc experienced an improvement in Partnership and Sexuality at 3 months. We noted opposite patterns in the Family Planning subscale, with an initial improvement only in switchers to rFVIIIFc.

TABLE 5 Proportion of patients who achieved minimal important difference in SF-36 at 3 months and 24 months in those with paired results

	Nonswitchers: rFVIII		Switchers to rFVIIIFc		Nonswitchers: rFIX		Switchers to rFIXFc	
	3 mo (n = 19)	24 mo (n = 21)	3 mo (n = 15)	24 mo (n = 9)	3 mo (n = 5)	24 months (*n* = 4)	3 mo (n = 9)	24 mo (n = 9)
PCS	6 (32)	9 (43)	3 (20)	1 (11)	2 (40)	1 (25)	5 (56)	4 (44)
MCS	4 (21)	5 (24)	7 (47)	4 (44)	1 (20)	0	2 (22)	4 (44)
Physical function	7 (37)	10 (48)	6 (40)	2 (22)	1 (20)	1 (25)	4 (44)	3 (33)
Role physical	6 (32)	8 (38)	9 (60)	4 (44)	0	1 (25)	3 (33)	5 (56)
Bodily pain	4 (21)	7 (33)	5 (33)	2 (22)	2 (40)	1 (25)	5 (56)	5 (56)
Social functioning	4 (21)	7 (33)	7 (47)	4 (44)	1 (20)	0	4 (44)	3 (33)
Mental health	5 (26)	8 (38)	8 (53)	3 (33)	1 (20)	1 (25)	5 (56)	3 (33)
Role emotional	3 (16)	4 (19)	7 (47)	4 (44)	0	0	2 (22)	2 (22)
Vitality	8 (42)	6 (29)	4 (27)	2 (22)	2 (40)	0	4 (44)	2 (22)
General health	6 (32)	9 (43)	5 (33)	1 (11)	3 (60)	1 (25)	4 (44)	5 (56)

Abbreviations: MCS, Mental Component Summary; PCS, Physical Component Summary.

3.8 | Treatment burden

Our cohort had high levels of treatment satisfaction at baseline, with a mean TSQM-9 score of 47 ± 8 in patients who switched to rFIXFc and 44 ± 5 in those who switched to rFVIIIFc, out of a maximum score of 59 indicating extreme satisfaction. Treatment satisfaction remained stable in switchers to rFIXFc and in nonswitchers remaining on SHL-FIX (Supporting Information). In contrast, switchers to rFVIIIFc experienced improved treatment satisfaction score from 44 at baseline, to 47 to 48 at 3 months and 24 months (60%-70% improved over one-half of a SD), whereas those remaining on SHL-FVIII had no changes (48-49) throughout the study (Supporting Information).

3.9 | Patient preference

At the end of the study, all patients (9/9) who switched to rFIXFc and 86% (6/7) of patients who switched to rFVIIIFc and completed the preference questionnaire preferred EHL over SHL concentrates. Among the patients who remained on SHL-FVIII/FIX and completed patient preference questionnaire, 2 of 2 (100%) persons with hemophilia B and 9 of 16 (56%) persons with hemophilia A stated that in retrospect they would have made the same decision to remain on SHL factor concentrates. On the other hand, 7 of 16 (44%) FVIII nonswitchers indicated at the end of study that they would have made the decision to switch to rFVIIIFc.

4 | DISCUSSION

In this Canadian prospective multicenter study, we assessed changes in HRQoL and other PROMs in a small cohort of persons with hemophilia who switched to rFVIIIFc/rFIXFc in a real-world setting, compared to those who remained on SHL-FVIII/FIX. We demonstrated a small improvement in overall HRQoL (Haem-A-QoL total score) in both switchers to rFIXFc and rFVIIIFc at 3 months and 12 months, over a quarter of rFIXFc patients met the responder definitions for a meaningful improvement. In addition to improved overall HRQoL, we observed meaningful improvements at 3 months in (i) physical functioning and activities, (ii) mental health, and (iii) social functioning following the switch to rFIXFc/rFVIIIFc, in the ability to engage in normal daily activities and chronic pain in switchers to rFIXFc, and in treatment satisfaction in switchers to rFVIIIFc. We did not observe meaningful changes in work impairment following a switch to EHL products, likely reflecting the fact that participants were well controlled on prophylaxis with SHL-FVIII/FIX, as reflected in low baseline work impairment. This ceiling effect must be taken into consideration when evaluating results of PROMs following a switch from SHL to EHL products in a population who already achieved low bleeding rates due to effective prophylaxis with SHL products. Most PROM instruments were developed in the era of SHL-FVIII/FIX, and hence are more likely to demonstrate responsiveness following switches from episodic (on-demand) to prophylactic treatment, than switches from SHL to EHL concentrates. What is perhaps more powerful is the end-of-study patient preference questionnaire, where 15 of 16 switchers indicated their preference for EHL over SHL concentrates. This provides a compelling argument that current PROMs may not be responsive to patient-relevant changes in populations well established on SHL prophylaxis.

While we did not perform inferential statistical testing in this small real-world study and focused on clinical relevance (based on MIDs or responder definitions), we observed similar magnitude of improvements in the Haem-A-QoL scores after switching to EHL products as reported in the phase 3 trials.[19–21] We observed a mean change in the Haem-A-QoL total score between −5.0 and −4.6 at 3 months and 12 months after switching to rFIXFc, with 29% achieving the responder definition threshold. This is comparable to

findings from the phase 3 trial (B-LONG) of rFIXFc, which reported a significant improvement in the Haem-A-QoL total score (−6.5; 44% achieved the responder definition) from baseline to 26 weeks in the weekly prophylaxis arm.[19] While one-half of patients received episodic prestudy treatment, a significant improvement in the Haem-A-QoL total score was observed in both prestudy prophylaxis (−5.5) and episodic (−7.5) groups.[19] In another prelicensure clinical trial of Rebinyn/Refixia (N9-GP; paradigm 2), adults who switched from SHL (54% episodic) to prophylaxis with N9-GP 40 IU/kg once weekly experienced a significant improvement in the Haem-A-QoL total score (−6.4).[20] The improvement in HRQoL is likely contributed by a marked reduction in ABR from 12.5 (previous episodic) and 4.0 (previous prophylaxis) to 1.0 following prophylaxis with 40 IU/kg weekly.[22] Similarly, following switch to rFVIIIFc, we observed a mean change in the Haem-A-QoL total score between −2.3 and −6.1 at 3 and 12 months (12% met the responder definition threshold). This is comparable to the mean reduction of −3.2 (24% met the responder definition) from baseline to week 28 reported in the rFVIIIFc individualized prophylaxis arm of the phase 3 A-LONG study.[19] In another prelicensure trial of Esperoct (N8-GP; pathfinder 2), adults who switched from SHL (15% episodic) to prophylaxis also reported statistically significant improvement in the Haem-A-QoL total score (−2.3), with achievement of the responder definition in 24%.[21] While the clinical trials typically used a follow-up period <1 year, our study purposefully included a 24-month longitudinal follow-up, demonstrating marked attenuation of initial improvements. This is likely attributable to the phenomenon of response shift, changes in individuals' self-evaluation of their quality of life due to changes in internal standards, values, or conceptualization of the measured construct.[3] While playing a role in patients' adaptation to chronic illness, response shift could result in a discrepancy between PROMs and true changes.[3]

This study aimed to fill an important gap in our understanding of PROMs in the era of EHL factor concentrates. Most studies have thus far focused on the impact of EHL concentrates on the most relevant outcomes from the lens of health care providers (ABRs, target joints, joint scores) or payers (factor usage). Few studies, largely derived from clinical trials, have examined the impact of switching on outcomes that may be more meaningful for patients and families. Recently, the International Standard Outcomes Set working group proposed a set of 10 PROMs, focusing on what increases value for patients and families receiving hemophilia care.[4] While we designed this study prior to its publication, as a proof of concept, we mapped our PROMs to the framework proposed by the working group (Table 1). We feel that inclusion of different dimensions of PROMs is critical, not only to assign value to meaningful patient outcomes (eg, productivity, physical activity) not traditionally included in trials, but also to better discern the benefits of prophylaxis with EHL compared with SHL-FVIII/FIX.

While the role of PROMs are becoming more important in the rapidly evolving therapeutic landscape for persons with hemophilia, our study highlighted limitations inherent in existing instruments. First, the ability of existing PROM instruments to detect significant changes is hindered by responsiveness to change and ceiling effect. Ceiling effects have been highlighted in CHO-KLAT version 2.0 for boys <18 years of age,[23] and in the treatment satisfaction questionnaire Hemo-Sat.[21] There are ongoing efforts in revising selected PROMs to improving their responsiveness in the era of EHL products, such as the recent development of CHO-KLAT version 3.0.[24] Second, responsiveness to change is also affected by differential time periods assessed across different instruments (eg, 7-day recall period in WPAI+CIQ:HS and IPAQ, compared with a 4-week recall period in SF-36). Third, not all PROMs are optimized for measuring the burden of administration of hemostatic agents (eg, frequency of intravenous injections) or relevance for specific individuals (eg, School and Work or Family Planning subscale in the elderly). Personalized PROMs and computer adaptive testing platforms may reduce burden of administering cumulative instruments, improve discriminatory ability, and increase relevance to individual patients' needs.[25] One example is the Patient-Reported Outcomes Measurement Information System item banks, although further work is needed to validate them in persons with hemophilia.[25] Goal attainment scaling is another adaptive and novel approach to PROM personalization, where the clinician-patient pair selects a list of meaningful goals for the individual, embedded in a measurement scale, which may offer greater responsiveness to small changes.[26] Finally, comparing HRQoL scores between chronic disease populations to the normative population (such as SF-36) can be confounded by a "disability paradox." People living with a chronic complex disease such as hemophilia may overestimate self-reported levels of health states due to reprioritization and recalibration of values and needs, recently demonstrated in a discrete choice experiment using the EuroQoL 5-Dimensions.[27]

Limitations of our study are several-fold. First, the power and precision of our study are limited by our small sample size along with missing data. As a result, we focused on clinically meaningful differences based on established MIDs and responder definitions. In addition, due to the nonrandom nature of missing data, incomplete data could create a bias (eg, patients with good HRQoL are more likely to complete 24-month questionnaires). Second, our study enrolled predominantly adult switchers to rFVIIIFc/rFIXFc, limiting the generalizability of our findings. Third, PROMs are subjective in nature and susceptible to bias in an open-label study of a novel agent. Fourth, the study was susceptible to confounding. We did not collect social determinants of health such as income and educational attainment, which may impact quality of life or the decision to switch to rFVIIIFc/rFIXFc. Finally, there was selection bias between switchers to EHL and nonswitchers, rendering the groups not directly comparable. Some older adults may be averse to changes or adopting novel technology, hence a bias toward patients who had higher ABR among switchers to rFVIIIFc/rFIXFc. We observed improvements in HRQoL even in nonswitchers, possibly explained by the effect of participating in the observational study, as well as by cointerventions (increased adoption of personalized, pharmacokinetic-guided prophylaxis during the study period).

5 | CONCLUSION

Our multicenter observational study demonstrated a meaningful improvement in the overall HRQoL in over a quarter of patients switching to rFIXFc, and a small proportion of patients switching to rFVIIIFc, mainly derived from improved physical function and activities, but also from improved mental health and social functioning. Our real-world study demonstrated the phenomenon of response shift, with attenuation of initial benefits as measured by validated PROMs by 24-month follow-up. On the other hand, the overwhelming majority of switchers voiced a preference for EHL over SHL products at the end-of-study visit, providing compelling evidence that current PROM scores do not reflect patients' responses to novel therapy in their entirety. Improvement of existing PROMs such as an updated CHO-KLAT version 3.0 for use in persons with hemophilia < 18 years of age and development of new tools are imperative to enhance the responsiveness over time with the advent of EHL concentrates and nonfactor hemostatic agents such as emicizumab for use in long-term prophylaxis of persons with hemophilia.

RELATIONSHIP DISCLOSURE

HS attended advisory boards for Bayer, Novo Nordisk, Octapharma, Pfizer, Sanofi, and Shire/Takeda; and received research support from Octapharma. MY has no conflicts of interest to declare. M-CP has received grant funding from Bayer and CSL Behring; has been an ad hoc speaker for Bayer, Novo Nordisk, and Pfizer; and attended advisory board meetings of Bioverativ/Sanofi, CSL Behring, Novo Nordisk, Pfizer, Roche, and Takeda. AL has received research grants from Bayer and Biovertiv/Sanofi; was a speaker/participant in advisory boards for Bayer, Novo Nordisk, Pfizer, and Shire/Takeda; was an ad hoc speaker for Bayer, Novo Nordisk, and Pfizer; attended advisory board meetings of Bioverativ/Sanofi, CSL Behring, Novo Nordisk, Pfizer, Roche, and Takeda; and received grant funding from Bayer and CSL Behring. KSR has received research funding from Roche; and was a speaker/participant in advisory boards for Celgene and Roche. MS has received consultancy/advisory board fees from Octapharma, NovoNordisk, Bayer, and Takeda. JW has received research funding from Bayer and honoraria from Bayer, Bioverativ, CSL Behring Novo Nordisk, Octapharma, Pfizer, and Shire. AI's institution has received project-based funding via research or service agreements with Bayer, CSL, Grifols, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, and Takeda. VB reports that he is Chair of the International Prophylaxis Study Group, a cooperative study group that is funded by education grants from Bayer Healthcare, Bioverativ/Sanofi, Novo Nordisk, Pfizer, Shire/Takeda, and Spark Therapeutics to the Hospital for Sick Children Foundation. He has received fees for participation in Advisory Boards/Education events supported by Amgen, Bayer, Novo. Nordisk, Pfizer, Roche and Shire/Takeda and for participation in Data Safety Monitoring Boards for Octapharma and Shire/Takeda. He has received investigator-initiated, industry-supported research grants from Novo Nordisk, Bioverativ/Sanofi and Shire/Takeda. In addition, he has a patent on the CHO-KLAT with royalties paid to the Hospital for Sick Children, Laurentian University, University of Manitoba, and Dr Victoria Price. MC has received research support from Bayer, Bioverativ/Sanofi, CSL Behring, Novo Nordisk, Octapharma, Pfizer, and Shire/Takeda; and honoraria for speaking/participating in advisory boards from Bayer, Biotest, Bioverativ/Sanofi, CSL Behring, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, Roche, and Shire/Takeda. RJK has received speaker and/or consultant fees from Agios Pharmaceuticals Inc., Amgen, Hoffmann La Roche LTD, Shire Pharma Canada ULC, Novo Nordisk Canada Inc, Octapharma AG, Takeda, and Sanofi-Genzyme. SJ has received research grants from Sanofi, Canadian Hemophilia Society; and honoraria from Pfizer/BMS, Takeda, Octapharma, Bayer, Roche; and consulting fees from Hemalytic.

AUTHOR CONTRIBUTIONS

HS designed the study, collected the data, performed data analysis and interpretation, and drafted the initial manuscript. MY coordinated data collection and critically reviewed the manuscript. M-CP, KSR, and RJK designed the study, collected the data, and critically reviewed the manuscript. AL, MS, JW, and AI, collected the data and revised the manuscript. VB collected the data, and critically reviewed the manuscript. MC performed data interpretation and critically reviewed the manuscript. SJ conceived the study, designed the study, obtained funding, collected the data, performed data interpretation, and critically reviewed the manuscript. All authors approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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