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ORIGINAL ARTICLE

Muskuloskeletal

LongHest project: A prospective, observational study of extended half-life treatment in the musculoskeletal health of patients with severe haemophilia A

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Abstract

Background: Prophylactic treatment is the gold standard in the treatment of patients with haemophilia. Prophylaxis with extended half-life (EHL) treatment has shown long-term safety and efficacy in patients with haemophilia.

Aim: To evaluate the efficacy of prophylaxis with EHL treatment in the frequency of haemarthrosis and musculoskeletal health in adult patients with severe haemophilia A.

Methods: Prospective cohort study. Forty-six patients with severe haemophilia A were recruited. The frequency of haemarthrosis (self-reports), joint condition (*Haemophilia Joint Health Score*), pain intensity (visual analogue scale), range of motion (goniometry), and strength (dynamometry) and muscle activation (surface electromyography) were evaluated. Three assessments were carried out: at baseline (T0), at 6 months (T1) and at 12 months following treatment (T2).

Results: There were significant changes in the within-subject effect in the frequency of haemarthrosis in elbow ($F(1.05;96.20) = 3.95$; $P < .001$) and knee ($F(1.73;157.99) = 9.96$; $P < .001$). Significant within-subject effect in elbow pain intensity ($F(2;182) = 63.51$; $P < .001$) was found. The mean values of the frequency haemarthrosis in elbow (from .66±1.01 to .04±.20) and knees (from .55±.68 to .33±.53) decrease after the period study. The intensity of elbow pain and (from 3.08±1.69 to 2.67±1.73), decrease after the 12-month follow-up period.

Conclusions: Prophylaxis with extended half-life treatment reduces the frequency of haemarthrosis in elbow and knee in adult patients with haemophilia. EHL treatment reduces the intensity of elbow pain in patients with haemophilic arthropathy.

KEYWORDS
extended half-life treatment, haemarthrosis, haemophilia, musculoskeletal health, prophylaxis

1 | INTRODUCTION

Patients with severe haemophilia A present FVIII plasma levels below 1% with spontaneous bleeding or haemorrhage associated with minimal trauma.[1] Recurrence of haemarthrosis induces synovial hypertrophy and cartilage damage, leading to gradual joint destruction known as haemophilic arthropathy.[2] The multifactorial process that leads to the establishment of haemophilic arthropathy is complex and to date is not entirely understood.[3] This arthropathy is the leading cause of morbidity and disability in patients with severe haemophilia.[1]

The standard treatment for severe haemophilia A is periodic IV FVIII replacement. The successful results of prophylaxis in these patients depends on the availability of clotting factor concentrates, trough FVIII levels, and the number of haemarthrosis events. Likewise, it is essential to understand bleeding trigger factors such as the amount of activity, synovial hypertrophy or previously existing arthropathy.[4] Early initiation of prophylactic treatment is recommended to protect the joints and prevent the development of arthropathy. Patients treated on an on-demand basis in which bleeding can be stopped, but arthropathy[5] is not prevented, have greater joint problems in knees, elbows and ankles.[1] However, in patients who have received prophylactic treatment, the ankles are the most affected joints.[4,6]

Cross-sectional studies have shown the benefits of prophylactic treatment in adolescent and adult patients in improving joint bleeding rates, joint function, and health-related quality of life.[6] However, structural joint damage exhibited by patients with haemophilic arthropathy in early adulthood continues to further develop despite subsequent prophylaxis, as a result of the irreversible degenerative process of this joint injury.[7]

Prophylactic regimens are customized based on factors such as haemorrhagic phenotype, FVIII pharmacokinetics or physical activity in each patient.[8] However, the short half-life of factor VIII concentrates, requiring frequent infusions, together with the limitations due to minimum blood levels of FVIII do not guarantee total protection against haemarthrosis.[9]

In the last decade, new FVIII concentrates have been designed to prolong their half-life: extended half-life treatment (EHL).[10] The addition of an Fc fusion protein to recombinant FVIII (rFVIIIFc) prolongs the half-life of recombinant FVIII.[11] The introduction of EHL has been increase 1.5-fold in factor VIII half-life and a 4-5-fold increase for factor IX half-life. This EHL can reduce the frequency of intravenous infusions by 30–35%,[12] maintaining a minimum FVIII level (3%) which is higher than with conventional products.[13] Data from ASPIRE study confirmed the long-term safety and efficacy of prophylactic treatment with rFVIIIFc. For more than 3 years, this treatment has shown to be effective in the prevention and management of bleeding in patients of all ages, reducing the frequency of bleeding and improving joint health.[14]

The main objective of the study was to assess the prophylactic efficacy of EHL treatment for reducing the frequency of haemarthrosis in adult patients with severe haemophilia A. The secondary objective was to analyse the prophylactic efficacy of EHL for reducing pain intensity, improving joint state, range of motion, and muscle strength and muscle activation in these patients.

2 | METHODS

2.1 | Study design

Observational prospective study to evaluate the efficacy of prophylactic treatment with EHL in patients with haemophilia A.

2.2 | Subject recruitment

The patients were recruited from the seven regions of Spain (Andalucía, Aragón, Castilla y León, Galicia, Murcia, País Vasco and Valencia) between July 2020 and September 2021.

Study inclusion criteria were: patients with severe haemophilia A (<1% FVIII); who in the month prior to their inclusion in the study had begun prophylactic treatment with rFVIIIFc; having a medical diagnosis of haemophilic arthropathy in at least three joints and scoring more than 3 points per joint on the *Haemophilia Joint Health Score*[15]; over 18 years of age; and no scheduled orthopaedic surgeries during the study period.

Exclusion criteria were antibodies to clotting factor concentrates (inhibitors); patients with gait disability; people with cognitive alterations that hinder or limit the understanding of the various evaluations; and patients who did not sign the informed consent document.

2.3 | Ethical considerations

The principal investigator explained to the patients the study objectives. After the oral presentation and delivery of the information sheet detailing study characteristics, all patients signed the informed consent document. This study was designed in accordance with the Helsinki provisions.

The study was approved by the Research Ethics Committee of the University of Murcia (ID: 2511/2019). Before starting patient recruitment, the research project was registered with the International Clinical Trials Registry (www.clinicaltrials.gov; NCT03914209). The Spanish Agency for Medicines and Other Health Products (AEMPS) classified the study as a "Prospective Follow-up Post-Authorization Study" (Resolution S-201901700001036).

2.4 | Clinical assessment

Patients were evaluated at baseline (T0), at 6 months (T1) and at 12 months follow-up (T2). All assessments were performed by the same physiotherapist, with years of experience in the evaluation and treatment of patients with haemophilia, blinded to which conditions.

The primary variable of the study was the frequency of joint bleeds. Secondary variables were joint health, pain intensity, range of motion, and muscle strength and activation.

The frequency of joint bleeding was controlled by a self-reporting system made available to patients at baseline. All patients were given a self-reporting register where they had to keep a record of the incidence of haemarthrosis during the period study. Self-reports included questions on the location, duration and onset of symptoms. In the event of haemarthrosis, they also included closed-ended questions, with closed-ended responses, about the main clinical manifestations (pain, inflammation, functional limitations, warmth, etc.).[16] Likewise, weekly rFVIIIFc dosing data (in IU) and dose administration intervals (in days) were collected in the three evaluations, based on the medical, clinical and pharmacokinetic criteria prescribed by each patient's haemophilia reference center.[14]

The joint health of knees, ankles and elbows was evaluated using the *Haemophilia Joint Health Score* (HJHS), version 2.1. This scoring system was designed to assess joint deterioration in paediatric patients with haemophilia.[15] A recent study shows the validity of this scoring in adults patients and provides high internal reliability (Cronbach's α = .88).[17] The scale measures eight items: swelling, duration of swelling, atrophy and muscle strength, crepitus, mobility and joint pain. The results of this scale express the degree of joint deterioration in patients with haemophilia ranging from 0 (joint without degenerative injury) to 20 (maximum joint damage) points.

The intensity of joint pain in elbows, ankles and knees was measured with the visual analogue scale.[18] This scale has shown moderate reliability (ICC: .60–.77) [19] in patients with chronic musculoskeletal pain. Its scores range from 0 to 10 points (from no pain to the maximum pain perceived by the patient).

A goniometer with two-degree increments measured the range of motion. This measuring instrument has shown good intra-observer reliability in elbow (ICC: .945 – .973),[20] knee (ICC: .91 – .99)[21] and ankle (ICC: .86 – .90).[22] Different joint measurement protocols were used for the evaluation of elbows,[23] knees[24] and ankles.[25] The unit of measurement employed is the degree, whereby the higher the degrees, the greater the range of motion.

Muscle strength was measured with a pressure dynamometer (*Lafayette Manual Muscle Tester* 01165).[26] The dynamometer was placed perpendicular to the site being evaluated. The patient was asked to conduct two 5-s maximum isometric contractions, with a 30-s break in between, against the dynamometer held by the evaluator.[27] Muscle strength of the quadriceps, hamstrings, biceps and triceps brachii, and tibialis anterior and gastrocnemius muscles was evaluated. For all measurements the rater instructed the patient in a standardized manner for the performance of the contractions (for example: "push, push… relax"). The mean value of the measurements obtained was used for the analysis of muscle strength data.[28] All measurements were performed bilaterally. Newton centimetre (N/cm^2) is the unit of measurement used by this instrument.

Muscle activation was evaluated by surface electromyography (surface EMG; *Shimmer Sensing, Dublin, Ireland)*. The electrodes were placed according to surface electromyography use recommendations, after shaving and cleaning the skin with alcohol.[29] Bipolar rectangular silver/silver chloride (Ag/AgCl) electrodes were used, measuring 28 × 44 mm (Ambu® WhiteSensor 4200 model) with a 46 mm^2 measurement area, 2 cm apart.[30] All patients received the same verbal stimulus to obtain maximum muscle strength.

2.5 | sEMG analysis

The reliable and validated surface electromyography (sEMG) mDurance® system (mDurance Solutions SL, Granada, Spain) was used to record muscle activity during a functional task (isokinetic knee extension) in vastus lateralis (ICC > .81) and rectus femoris (ICC > .762), by comparing with a reference sEMG system (Delsys® system).[31] Muscles evaluated were the quadriceps, gastrocnemius and soleus, in both lower limbs.

The mDurance® system (mDurance Solutions SL, Granada, Spain) consists of three parts: (a) a Shimmer3 EMG unit (Realtime Technologies LtD, Dublin, Ireland) which is a bipolar surface electromyography sensor for the acquisition of muscle activity. Each Shimmer3 has two channels, with a 1024 Hz sampling rate. Shimmer3 applies an 8.4 Hz bandwidth, while the EMG signal resolution is 24 bits, having an overall amplification of 100–10000 V/V; (b) mDurance Android application which receives data from Shimmer3 and sends it to a cloud service; and (c) mDurance cloud service where data is stored, filtered and analyzed.[31]

The raw data was processed and filtered using a fourth-order Butterworth bandpass filter with a 20–450 Hz cut-off frequency. The signal was smoothed using a window size of .025s root mean square (RMS) and .0125 s overlap between windows.[31] The main variable recorded for muscle activity was the mean RMS expressed in microV of the middle third of the isometric contraction. Start and end of the signal were identified using a threshold method and this was verified visually afterwards. The unit of measurement employed is the microV (μV), whereby the higher the degrees, the greater the muscle activity.

Prior to recruiting the patients, a pilot study was conducted to determine interobserver reliability. This analysis was performed on the variables range of motion, muscle strength and muscle activation. Five patients with haemophilia not included in the study were evaluated. High intra-observer reliability was observed for muscle strength and range of motion of elbows and knees (ICC > .97), and quadriceps muscle activation (ICC > .98). Moderate – high intra-observer reliability was observed in ankle range of motion (ICC = .80) and gastrocnemius and soleus muscle activation (ICC = .79–.80).

2.6 | Sample size

The sample size was calculated using the statistical package G * Power (version 3.1.9.2; Heinrich-Heine-Universität Düsseldorf, Germany). Assuming a mean effect size (d = .60), with an alpha level (type I error) of .05 and a statistical power of 99% (1-β = .99), a sample size of 38 patients with haemophilic knee arthropathy was estimated. Predicting

a potential 20% of patient dropouts during the follow-up year, 46 adult patients with severe haemophilia A were recruited from seven different locations.

2.7 | Statistical analysis

The statistical analysis was carried out with version 19.0 of the statistical package SPSS for Windows (IBM Company, Armonk, NY, USA). The intra-observer reliability analysis was performed using the intraclass correlation coefficient. Descriptive statistics of central tendency and dispersion (mean and standard deviation) of the study variables were calculated. The analysis of the within-group effect was performed with the repeated measures ANOVA test. The error rate of the significance level was controlled using the Bonferroni correction. When Mauchly's sphericity test was significant, the Greenhouse-Geisser correction coefficient was used.

Changes from T2 to T0 was analysed using a paired-samples t-test. The effect size of the changes observed after the intervention was calculated using Cohen's d standardized mean difference formula, being classified as large (d > .80), medium (d > .50) or small (d > .20).[32] The minimum detectable change (MDC) was calculated by estimating the standard error of measurement (SEM). SEM was calculated using the formula: SEM = SDpre $*$ $\sqrt{}$1-ICC.[33] The intraclass correlation coefficient was used as measure of reliability.[34] Based on SEM, MDC was obtained (MDC = Z-score $*$ $\sqrt{}$ 2 $*$ SEM). The confidence level was set at 95% (Z score = 1.96).[35] An intent-to-treat analysis has been carried out in this study. The significance level of the study was .016 (α = .05 / 3).

3 | RESULTS

Forty-six patients with haemophilia initially took part in the study. During the study period, one patient dropped out due to unforeseen surgery and another patient failed to attend the last evaluation appointment for personal reasons. The mean age of the patients was 38.62 (SD: 6.42) years. All patients included in the study received the same EHL (efmoroctocog alfa). A significant decrease in weekly EHL dosage was observed throughout the study year (6434.78 [SD: 980.97] vs. 5913.04 [SD: 1244.11] IU; 95% CI = 281.38 – 762.09; $P < .001$). Significant differences were found in the number of weekly infusions between T0 and T2 assessments (2.35 [SD: .48] vs. 1.83 [SD: .48] days weekly; 95% CI = .33; .70; $P < .001$). Table 1 shows the descriptive characteristics of patients.

TABLE 1 Descriptive characteristics of the patients included in the study

Variables	Mean	Standard deviation
Age (years)	38.62	6.42
Weight (kg)	85.43	7.94
Height (cm)	177.43	4.82
Body mass index (kg/m^2)	26.78	4.26
Weekly dose (IU)		
Baseline	6434.78	980.97
1-year follow-up	5913.04	1244.11
Weekly infusions (days)		
Baseline	2.35	.48
1-year follow-up	1.83	.49
	n	%
Marital status		
Single	30	65.2
Married	14	30.4
Divorced	2	4.4
Educational level		
Basic studies	11	23.9
Professional training	17	37.0
University studies	18	39.1
Employment status		
Employee	18	39.1
Unemployed	17	37.0
Businessman	4	8.7
Laboral inability	7	15.2

3.1 | Elbow joint

In the repeated measures analysis we observed significant within-subject effect in frequency of joint bleedings ($F(1.05;6.20) = 3.95$; $P < .001$), and pain intensity ($F(2;182) = 63.51$; $P < .001$). When comparing the last assessment with baseline (T2-T0) there were significant changes in the frequency of haemarthrosis (MD = -.62; 95%CI = .42; .81; $P < .001$) and pain intensity (MD = -.41; 95%CI = .32; .51; $P < .001$). Table 2 shows the changes in elbow joint.

3.2 | Ankle joint

No significant difference ($P < .016$) was reported in dependent variables, upon comparing the three assessments in the repeated measures analysis. No significant changes were found at the T2–T0 comparison. Table 3 shows the results of the repeated measures analysis and changes in ankle joint.

3.3 | Knee joint

In the repeated measures analysis we observed significant within-subject effect in frequency of joint bleedings ($F(1.73;157.99) = 9.96$; $P < .001$). When comparing T2 – T0 there were significant changes in the frequency of haemarthrosis (MD = -.22; 95%CI = .10; .35; $P < .001$)

TABLE 2 Analysis of the statistics, within-subject effect and changes after study period in elbow joint

	Mean (standard deviation)			Within-subject effect		Changes between T2 and T0			
Variables	T0	T1	T2	F	Sig.	MD (95%CI)	Sig.	ES	MDC (MDCp)
Haemarthrosis (number)	.66 (1.01)	.00 (.00)	.04 (.20)	3.95	.00**	-.62 (-.81; -.42)	.00**	-.85	-2.55 (26.98)
Joint status (0 -20)	9.10 (2.78)	8.98 (2.69)	8.98 (2.58)	1.82	.17	-.12 (-.28; .04)	.16	-.04	-1.92 (13.04)
Intensity of joint pain (0 – 10)	3.08 (1.69)	2.86 (1.68)	2.67 (1.73)	63.51	.00**	-.41 (-.51; -.32)	.00**	-.23	-1.35 (28.26)
Range of motion (degrees)	116.36 (2.96)	116.54 (2.87)	117.22 (2.93)	2.85	.07	.86 (-.02; 1.72)	.05	.29	1.14 (34.78)
Biceps strength (N)	166.59 (37.39)	167.23 (36.97)	167.21 (37.30)	2.64	.07	.62 (.04; 1.20)	.03	.01	5.35 (21.73)
Triceps strength (N)	244.63 (30.75)	247.32 (25.24)	241.57 (30.17)	2.25	.12	-3.06 (-9.68; 3.55)	.36	-.09	-12.06 (15.21)

T0: Outcome measures at the baseline; T1: Outcome measures after the 6-months period: T1: Outcome measures at 12-months period (T2); Sig.: significance; MD: means difference; 95%CI: 95% confidence interval; ES: effect size; MDC: minimal detectable change; MDCp: proportion of minimal detectable change.
*Significant difference between assessments ($P < .016$).
**Significant difference between assessments ($P < .001$).

TABLE 3 Analysis of the statistics, within-subject effect and changes after study period in ankle joint

	Mean (standard deviation)			Within-subject effect		Changes between T2 and T0			
Variables	T0	T1	T2	F	Sig.	MD (95%CI)	Sig.	ES	MDC (MDCp)
Haemarthrosis (number)	.39 (.69)	.26 (.46)	.25 (.48)	3.95	.03	-.14 (-.27; -.01)	.04	.23	1.86 (8.69)
Joint status (0 -20)	8.47 (2.08)	8.33 (2.11)	8.34 (2.27)	2.45	.09	-.13 (-.29; .03)	.10	.05	1.78 (17.39)
Intensity of joint pain (0 – 10)	3.57 (2.80)	3.29 (2.64)	3.25 (2.57)	4.03	.04	-.32 (-.61; -.03)	.03	.11	2.46 (19.56)
Range of motion (degrees)	33.19 (.73)	33.91 (.64)	33.95 (.63)	4.17	.026	.76 (.03; 1.48)	.04	-1.11	1.25 (60.86)
Triceps strength (N)	256.35 (21.71)	256.36 (20.53)	256.09 (22.52)	.04	.89	-.25(-2.68; 2.17)	.83	-.01	6.86 (26.08)
Tibial strength (N)	284.94 (30.47)	287.61 (31.45)	288.96 (32.52)	3.51	.04	4.01 (.38; 7.65)	.03	.12	8.38 (63.04)
Internal gastrocnemius activation (μV)	57.99 (42.35)	57.00 (39.14)	56.82 (39.94)	2.36	.10	-1.17 (-2.44; .09)	.07	.02	5.70 (21.73)
External gastrocnemius activation (μV)	66.03 (31.32)	66.41 (32.94)	66.80 (32.66)	3.49	.05	.77 (.11; 1.43)	.02	-.02	4.90 (10.86)
Soleus activation (μV)	38.20 (19.46)	37.72 (18.08)	37.55 (18.65)	1.52	.22	-.64 (-1.56; .26)	.16	.03	4.59 (23.91)

T0: Outcome measures at the baseline; T1: Outcome measures after the 6-months period: T1: Outcome measures at 12-months period (T2); Sig.: significance; MD: means difference; 95%CI: 95% confidence interval; ES: effect size; MDC: minimal detectable change; MDCp: proportion of minimal detectable change.
*Significant difference between assessments ($P < .016$).
**Significant difference between assessments ($P < .001$).

and hamstring strength (MD = -.94; 95%CI = .18; 1.70; $P = .01$). Table 4 shows the changes in knee joint.

4 | DISCUSSION

This study aimed to evaluate the prophylaxis efficacy with EHL treatment in patients with severe haemophilia A over a 12-month follow-up period. Our results report improvements in terms of frequency of haemarthrosis and intensity of joint pain.

In recent years, the scenario related to haemophilia A treatment has changed enormously with the widened use of prophylaxis and patient-specific care. Customized dosing of FVIII concentrates is essential in the treatment of severe haemophilia A. Earlier studies [14,36] have confirmed the long-term safety and efficacy of rFVIIIFc in patients with severe haemophilia A. In our research, as the study period progressed,

TABLE 4 Analysis of the statistics, within-subject effect and changes after study period in knee joint

	Mean (standard deviation)			Within-subject effect		Changes between T2 and T0			
Variables	T0	T1	T2	F	Sig.	MD (95%CI)	Sig.	ES	MDC (MDCp)
Haemarthrosis (number)	.55 (.68)	.32 (.49)	.33 (.53)	9.96	.00**	-.22 (-.35; -.10)	.00*	.36	1.73 (15.21)
Joint status (0 -20)	7.02 (2.16)	7.07 (2.13)	7.11 (2.10)	1.61	.20	.08 (-.01; .19)	.10	-.04	1.53 (15.21)
Intensity of joint pain (0 – 10)	2.15 (1.26)	2.07 (1.30)	2.07 (1.30)	3.40	.04	-.07 (-.16; .004)	.06	.06	1.29 (17.39)
Range of motion (degrees)	120.91 (1.46)	121.06 (1.47)	121.06 (1.45)	1.04	.33	.15 (-.15; .45)	.32	-.10	1.05 (8.69)
Quadriceps strength (N)	268.88 (24.97)	269.26 (25.48)	269.74 (25.95)	2.14	.12	.85 (-.07; 1.79)	.07	-.03	4.38 (36.95)
Hamstring strength (N)	253.29 (24.85)	252.82 (25.52)	252.35 (25.29)	3.17	.05	-.94 (-1.70; -.18)	.01*	.03	4.36 (8.69)
Rectus femoris activation (μV)	89.93 (86.86)	91.57 (87.01)	90.59 (87.01)	3.51	.05	.66 (-.88; 2.22)	.39	.01	8.16 (23.91)
Vastus lateralis activation (μV)	91.23 (101.39)	91.62 (101.14)	91.54 (101.39)	2.50	.08	.31 (-.06; .69)	.10	.00	.00 (67.39)
Vastus lateralis activation (μV)	100.96 (115.84)	100.93 (116.12)	100.50 (115.60)	2.12	.12	-.46 (-.91; -.01)	.04	.00	9.43 (6.51)

T0: Outcome measures at the baseline; T1: Outcome measures after the 6-months period: T1: Outcome measures at 12-months period (T2); Sig.: significance; MD: means difference; 95%CI: 95% confidence interval; ES: effect size; MDC: minimal detectable change; MDCp: proportion of minimal detectable change.
*Significant difference between assessments ($P < .016$).
**Significant difference between assessments ($P < .001$).

the dosage and frequency of weekly rFVIIIFc infusions was adjusted by hematologists according to the pharmacokinetic and clinical values recorded for each patient. This customized treatment was associated with a decrease in the frequency of haemarthrosis in elbow and knee joints. Our results are consistent with those reported by the ASPIRE study,[14] where the rFVIIIFc dosage according to the patient's pharmacokinetic profile achieved an improvement in the annual bleeding rate of patients included in that study. Similarly, Wang and Young reported a significant reduction in the annualized rate of haemarthrosis in 17 patients with haemophilia on rFVIIIFc prophylaxis. This rate was despite the dosing frequency adjustment (from two weekly infusions to 1 dose every 5 days), and the decrease in weekly factor intake in 53% of patients on rFVIIIFc prophylaxis.[37]

Continued prophylaxis with FVIII concentrates may improve joint health, health-related quality of life, activity, and pain in patients with severe haemophilia, regardless of age and previous joint damage [7]. Chronic pain is typically present in arthropathy, limiting the performance of daily activities in people with haemophilia. Witkop et al. [38] reported that 20% of patients with haemophilia experience acute pain, 34% chronic pain, and 32% both types of pain. Our study reported a significant decrease in pain intensity in elbow joints. To understand the improvement achieved in a variable as disabling as pain, the key may be the lower frequency of haemarthrosis during the study period. The improvement in the rate of haemarthrosis, and also therefore a reduced synovial inflammation and improved function, may explain the improvement in pain intensity over such a long period of time.

Improved musculoskeletal outcomes is an important measure of the effectiveness of prophylactic treatment for haemophilia A. Oldenburg et al [6] found how the rate of haemarthrosis reduced in adult and adolescent patients treated with prophylaxis compared to patients following an on-demand treatment. Similarly, magnetic resonance imaging analysis suggested the structural preservation of joints in patients treated with prophylaxis, especially when treatment begins during childhood. Manco-Johnson et al.[7] reported a 94% reduction in the frequency of bleeding in a group of patients on prophylaxis for 3 years, but despite their poorer joint condition at the beginning of the study, their MRI evaluation did not improve. However, the progression of structural damage was reduced in the younger patients, under 20 years old, suggesting that prophylaxis may stop osteochondral damage in younger subjects. In contrast to the results obtained with imaging techniques, prophylaxis has shown its effectiveness in the results of the physical evaluation of joint health.[7] Although joint deformities do not improve with prophylaxis, the absence of bleeding allows a higher level of activity in patients with haemophilia. Prophylaxis is likely effective in preventing haemophilic arthropathy, but its effectiveness for stopping or reversing its progression after the onset of joint damage is not clear. This information is consistent with the results observed in this study in the joint health.

Long-term treatment with rFVIIIFc has been associated with improved joint health.[39] Oldenburg et al. [36] disclosed that inflammation, range of motion and strength in the amended version of the *HJHS* were the variables most contributing to the improvement of joint health in patients with haemophilia following prophylactic treatment

with rFVIIIFc. However, our study provided no statistically significant changes in joint status, range of motion and muscle strength. Deeper knowledge is needed about the effect of the Fc domain of rFVIIIFc on joint health. Analysis of the prolonged half-life or potential anti-inflammatory properties of IgG Fc mediated via the Fc receptor[40] could shed light on the reasons behind these improvements.

4.1 | Study limitations

One of the main limitations of the study is the absence of more objective instruments for the quantification of joint health (for example, imaging techniques). Prophylaxis with rFVIIIFc provides an effective approach for the prevention of acute bleeding, strengthening protection during intense physical activity.[39] Another limitation is the failure to assess joint functionality, something that would allow us to evaluate joint deterioration in these patients. The absence of an analysis of patient activity in order to relate the functional improvements with prophylactic treatment and the rate of haemarthrosis is another limitation of our study.

5 | CONCLUSIONS

Prophylaxis with EHL treatment improves the frequency of haemarthrosis in elbows and knees in adult patients with haemophilia. Continued administration of EHL can reduce the intensity of joint pain in patients with elbow haemophilic arthropathy. At one-year follow-up no significant changes were reported in the ankle joint. It is necessary to carry out studies with longer follow-up periods to assess the impact of prophylaxis with EHL treatment in adult patients with haemophilic arthropathy.

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DISCLOSURES

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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