

Physical activity improved by adherence to prophylaxis in an Italian population of children, adolescents and adults with severe haemophilia A: the SHAPE Study

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Background. Physical activity in people with haemophilia (PWH) reduces the development of severe arthropathy, but it must be performed after regular, proper prophylaxis. Strict adherence to treatment is crucial to achieving effectiveness and established outcomes. The primary aim of this study was to collect prospective data on adherence to prophylaxis for over 36 months. A secondary aim was to verify whether adherence correlates with physical activity.

Materials and methods. Italian patients with severe haemophilia A treated on prophylaxis with octocog alfa were included in the study. Physical findings were assessed by the Haemophilia and Exercise Project (HEP)-Test-Q and the Early Prophylaxis Immunologic Challenge (EPIC)-Norfolk Physical Activity Questionnaire; orthopaedic status was assessed by the Hemophilia Joint Health Score (HJHS). Adherence was measured as percentage of empty vials returned with respect to the prescribed amount.

Results. Forty-two PWH were enrolled: 31% children, 21.4% adolescents, and 47.6% adults. Type, frequency and impact of physical activities differed among the three groups. The HEP-Test-Q showed the highest impairments in the domains "endurance" and "strength/co-ordination". Eight percent of patients were classified as adherent to prophylaxis. Among them, 50% had at least one bleeding episode in the year before enrolment; this percentage dropped during the three years of the study. While remaining stable in the "non-adherent" group, the HJHS score decreased in the "adherent" patients. The mean number of school/work days lost was lower in adherent patients (from 3.4±6.8 to 0.2±0.9) than in non-adherent ones.

Discussion. PWH with better orthopaedic scores reported better physical performance. Adherence to long-term prophylaxis proved to be high and correlated with a reduction in bleeds, target joints, school/work days lost, and with a performance improvement in endurance sports activities over time.

Keywords: severe haemophilia, physical activity, adherence to treatment, FVIII replacement therapy, orthopaedic haemophilia scores.

Introduction

Prophylaxis is the gold standard of treatment in patients with haemophilia A¹. The prophylaxis regimen reduces bleeding episodes and prevents or slows down

the development of arthropathy, which is a disabling complication of this condition²⁻⁵. The full benefit of prophylaxis in adults is still a subject of debate, but it is clear that preventive treatment improves quality of

life^{6,7}. However, the prophylaxis regimen is not without problems. The main challenges are related to the cost of this therapy for national health systems and the burden of frequent intravenous infusions. Especially in children, frequent intravenous infusions often require a central venous catheter implantation (CVC) likely to cause infections and thrombosis, as well as parents' or patients' acceptance of the procedure⁸.

Adherence to the prescribed prophylactic regimen is crucial to treatment efficacy⁹. Better adherence to prophylaxis seems to reduce chronic pain¹⁰. A phone interview survey conducted in the USA has already shown that only 58.8% of haemophilia patients follow the prescribed therapy¹¹. In other studies, adherence was higher, particularly in children under 12 years of age^{12,13}. Poorer adherence was associated with more breakthrough and target joint bleeds^{9,14}.

Studies have recently been carried out to assess which factors are associated with lower adherence to treatment. The transition from adolescence to adulthood is often related to a decrease in compliance; other factors for this decrease are the number of weekly infusions and socio-economic conditions^{15,16}.

Up to now, only a few prospective studies have evaluated adherence in haemophilia A patients, but no data on adherence of Italian haemophilia patients under a prophylaxis regimen^{17,18} are available.

In the past, PWH were discouraged from doing sports and physical activity due to a perceived risk of bleeding, but a recent review showed¹⁹ how patients with congenital bleeding disorders can benefit from exercise. All haemophilia patients are encouraged to play sport from childhood, especially if they receive adequate prophylaxis.

The purpose of this study was to collect prospective data on adherence to primary and secondary prophylaxis over 36 months in a population of severe haemophilia A (FVIII:C <1%) sufferers who had been under prophylaxis with octocog alfa for at least 6 months, and to assess whether the prophylaxis regimen can improve orthopaedic scores and patient performance during physical activity.

Materials and methods

Patients

The SHAPE study is a prospective study that included all subjects with severe haemophilia A (FVIII:C <1%) treated at 14 Italian haemophilia centres with a long-term prophylaxis regimen (25-40 IU/kg 2 or 3 times a week) with octocog alfa (Helixate NexGen; CSL-Behring SpA, Milan, Italy) and started at least 6 months prior to study enrolment. Data collection began in January 2013 and ended in June 2016. All subjects were followed for 36 months from enrolment. This study was approved by the Ethics Committee of the participating haemophilia centres.

The patients were divided into three groups: 1) children (<12 years); 2) adolescents (12-18 years); 3) adults (>18 years).

Written informed consent was obtained from patients or from parents/caregivers for patients under 18 years prior to study entry.

Exclusion criteria were: 1) patients with a current or previous history of clinically significant inhibitor; 2) patients with liver cirrhosis or rapidly progressing liver disease; 3) patients with overt AIDS or severe and chronic concomitant diseases; 4) patients with platelet count <70×10⁹/L within one month of the inclusion visit; 5) patients treated with factor VIII (FVIII) concentrates other than octocog alfa; 6) patients treated with FVIII only on demand; 7) patients on prophylaxis for less than 6 months; 8) patients on prophylaxis less than twice a week; 9) patients participating in other experimental studies with any other drugs; 10) patients who refused to sign informed consent. Each subject was instructed to record the date, hour, dosage, and method of infusion in a special diary, as well as any other information about the infusions themselves.

Data collection

At enrolment, the following data were collected.

Demographic variables

Age and date of birth, gender, haemophilia A severity, type of genetic disorder; body weight, height, type of occupation, and education (if known).

Past and recent medical history

Date of first diagnosis of haemophilia A and residual FVIII:C activity; total number of therapy exposure days (ED) up to the date of the hospital visit during which the patient was included in the study; frequency of minor or major bleeding episodes occurring in the year before enrolment; use of blood components, blood products or other concentrates over the year before enrolment; type of prophylaxis indicated (primary, secondary), and prophylaxis regimen (when it was instituted, at what dosage and at what weekly frequency, previous regimen changes and the reason[s] for such changes); days of school/work lost in the year before enrolment in the study.

All the data collected reflect the information reported in the medical record and in each patient's diary.

Concomitant diseases and treatments

Viral hepatitis infections or HIV infections; occurrence of any drug adverse reactions and other concomitant pharmacological treatments.

Surgery and hospitalisation

Minor or major surgery with any possible changes

in the prophylaxis regimen; suspected adverse reactions (e.g. allergic reactions); development of inhibitors; school or work days lost, and number of days of hospitalisation. Dosage, frequency and duration of prophylaxis were established by the physicians of each centre participating in the study in consideration of the baseline characteristics of each patient. We also investigated the drug tolerability with strict adherence to the current standards in force and prepared an appropriate report according to both the pharmacovigilance criteria set forth in the current national legislation concerning already marketed drugs and the pharmacovigilance regulations adopted by the institution where the trial was performed. Evaluation of joint status was carried out through: 1) the Hemophilia Joint Health Score (HJHS)²⁰, which assessed swelling, duration of swelling, muscle atrophy, crepitus on motion, flexion loss, joint pain, and strength for each joint (the score obtained determined the severity of arthropathy); 2) the Gilbert Score²¹, which measures joint health (in the domain of body structure and function) of the joints most commonly affected by bleeding in haemophilia (knees, ankles, elbows).

From 6 to 36 months of follow up, patients were evaluated according to: any changes in prophylaxis regimen; number and type of bleeding events; variation in the values obtained with the HJHS score; total number of exposure days (ED) to octocog alfa; school/work days lost; and concomitant diseases.

Physical activity

At enrolment and during follow up, all patients were asked how often they did such sports activities as going to the gym, swimming or playing team sports, and what other hobbies they had, before and during the study. The physical activity performed by each subject was assessed by the standardised questionnaires (HEP-Test-Q and EPIC Norfolk Physical Activity Questionnaire)^{20,21}.

Adherence to prophylaxis

The primary variable of the study was defined as adherence to the prophylaxis regimen at the end of the observation period. Adherence to therapy was assessed by counting the empty vials of octocog alfa returned compared to those prescribed. During the study period the adherence rate was calculated on the previous year.

Following these results, we classified the enrolled patients under two groups:

- adherent: 75-100% empty vials returned;
- non-adherent: <75% empty vials returned.

Statistical analysis

Absolute and percentage (number [n], %) of subjects and related 95% confidence intervals (95% CI) were calculated for each level of therapy compliance (5 levels).

Absolute and percentage frequencies (n, %) of subjects adherent or non-adherent to the prophylaxis regimen with relevant 95% CI were calculated.

The association between adherence to the prophylaxis regimen (adherent vs non-adherent subjects) and demographic and socio-economic characteristics, general patient condition and patients' characteristics were evaluated using the χ^2 test and Student *t*-test at a significant level of $\alpha=0.05$ (two-sided).

The demographic characteristics, medical profile (concomitant diseases and therapies, clinical history, physical activity, etc.), and all the other detected variables of each patient were analysed by descriptive statistical methods. Data are shown as a mean \pm standard deviation, median, and range (minimum to maximum).

Data were analysed using the IBM SPSS programme (version 23; SPSS Inc., Chicago, IL, USA).

Results

Forty-two patients were enrolled in our study. Thirteen were children (31%), 9 (21.4%) were adolescents, and 20 (47.6%) were adults. Two patients dropped out during follow up. Thirty-seven percent of adults had a primary school diploma, 37% a secondary school diploma, and 26% a university degree; 68.4% of adults were employed, 10.5% were students, 10.5% were retired, and the remaining 10.6% were unemployed.

Only one adult had a body mass index >30. Nine patients were overweight, including two children and one teenager. Only 15% of patients had at least one comorbid condition (1 teenager and 5 adults). A prevalence of "chronic HCV-positive liver disease" was recorded in 3 cases, while there were 2 cases of "hypertension".

Eighty percent of patients adhered to the prophylactic regimen (95% CI: 66.1-93.9). According to age distribution, 83.3% (60.2-106.4) of children, 77.8% (47-108.6) of adolescents, and 78.9% (58.3-99.6) of adults were considered adherent. Stratification by age showed that adherence was remarkably similar in all patient groups. Data in relation to level of adherence and age distribution are shown in Table I.

Patients with a higher level of educational (university degree or high school graduation) showed a trend towards higher adherence to treatment (73 vs 26.7%) (odd ratio [OR] 3.17; $p=0.075$).

Among the adherent patients, 50.0% had at least one bleeding episode in the year before the beginning of the study. This percentage clearly dropped during the 3-year follow up: only 34.4% had a bleeding episode in the first year, 31.3% in the second, and 28.1% in the third year. Children, adolescents, and adults showed the same trend. In absolute terms, the number of bleeding events reported during the second year of the study was two-thirds lower than that in the first year in all the patients: 158 vs 43

Table I - Level of adherence according to age distribution.

Level of adherence	Age groups											
	Children			Adolescents			Adults			Total		
	N	%	95% CI [range]	N	%	95% CI [range]	N	%	95% CI [range]	N	%	95% CI [range]
None	1	8.3	[-45.8-62.5]	1	11.1	[-50.5-72.7]	2	10.5	[-32.0-53.1]	4	10	[-19.4-39.4]
Minimal	2	16.7	[-35.0-68.3]	-	-		2	10.5	[-32.0-53.1]	4	10	[-19.4-39.4]
Low	1	8.3	[-45.8-62.5]	1	11.1	[-50.5-72.7]	2	10.5	[-32.0-53.1]	4	10	[-19.4-39.4]
Medium	3	25	[-24.0-74.0]	3	33.3	[-20.0-86.7]	3	15.8	[-25.5-57.1]	9	22.5	[-4.8-49.8]
High	5	41.7	[-1.5-84.9]	4	44.4	[-4.3-93.1]	10	52.6	[21.7-83.6]	19	47.5	[25.0-70.0]
	12	100		9	100		19	100		40	100	

N: number; CI: confidence interval.

Table II - School/work days lost (per year within the study).

		Adherence											
		No						Yes					
		N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Year 1	Children	7	1.6	3	0	0	8	16	0.9	2.3	0	0	8
	Adolescents	4	12.5	15	0	10	30	15	6.3	15.8	0	0	60
	Adults	10	0	0	0	0	0	27	3.4	17.3	0	0	90
Year 2	Children	5	0	0	0	0	0	9	0.2	0.7	0	0	2
	Adolescents	2	0	0	0	0	0	12	0.6	1.5	0	0	5
	Adults	9	0	0	0	0	0	19	1.1	2.5	0	0	10
Year 3	Children	5	1	2.2	0	0	5	9	1.2	2	0	0	5
	Adolescents	3	1.7	2.9	0	0	5	11	0.5	1.5	0	0	5
	Adults	10	2.8	4	0	0	10	21	0.2	0.9	0	0	4

N: number; SD: standard deviation; Min: minimum; Max: maximum.

Table III - Physical activity according to adherence.

		Adherence				
		None	Minimal	Low	Medium	High
<i>Type of sport</i>						
	Hobby/leisure	3 (15%)	2 (10%)	2 (10%)	2 (10%)	11 (55%)
	Endurance sports	3 (14.3%)	2 (9.9%)	2 (9.9%)	3 (14.3%)	11 (52.4%)
	Athletic sports	2 (13.3%)	2 (13.3%)	1 (6.7%)	1 (6.7%)	9 (60%)
	Ball sports	2 (16.7%)	-	1 (8.3%)	2 (16.7%)	7 (58.3%)
<i>Impact of physical activity on joints</i>						
	None	3 (14.3%)	2 (9.5%)	2 (9.5%)	2 (9.5%)	12 (57.1%)
	Medium	2 (10%)	1 (5%)	2 (10%)	3 (15%)	12 (60%)
	High	1 (16.7%)	-	1 (16.7%)	2 (33.3%)	2 (33.3%)

in children/adolescents and 62 vs 34 in adults: (χ^2 test DF=3, χ^2 test value=29.21; $p<0.0001$).

The musculoskeletal clinical score measured by the Gilbert score was 6.9 ± 8.2 on average in "non-adherent" patients and 7.3 ± 1.10 in "adherent" ones. At the end of the study, there was a decrease in the average values for "adherent" and "non-adherent" patients, but there was no statistically significant difference between the two groups.

On average, the HJHS score decreased from 2.3 ± 3.2 to 0.1 ± 0.4 in "adherent" patients. It was not possible to compare the same score for "non-adherent" patients because of the low number of clinical assessments.

Over time, the number of the total target joints decreased for "adherent" patients from a baseline of 19 to a final value of 13, while numbers remained stable at 9 in the "non-adherent" group.

In the year before enrolment, the mean number of school/work days lost in adherent patients was 3.4 ± 6.8 in comparison to 8.5 ± 12.6 in the non-adherent group. At the end of the third year, the mean number of school/work days lost was 0.2 ± 0.9 in the "adherent" group in comparison to 2.8 ± 4.0 days in the "non-adherent" group (Table II).

Highly adherent patients did more sport and engaged in more physical activities with a medium impact on joints compared to patients with no or low adherence (Table III).

In this study, we noticed a difference between adolescents and adults in the type, frequency, and impact of physical activities undertaken. The HEP-Test-Q showed the highest impairments in the domain "endurance" (32.4% reported a *fair/poor* actual physical activity) and in the domain "strength and co-ordination" (47.2% could *never/seldom* carry out exhausting activities). PWH with a better orthopaedic joint status reported better subjective physical performance. No severe adverse reaction that could be related to medication was reported during the study.

Discussion

Our study prospectively assessed adherence in Italian haemophilia A patients on long-term prophylaxis and correlated it with physical activity.

A well-conducted prophylaxis can prevent the development of arthropathy^{22,23}. In order to achieve this objective, the patient's strict compliance with the therapeutic program directed by the physician is necessary.

In the literature, there are many retrospective or cross-sectional studies assessing adherence to therapy in haemophiliacs. Due to different methods of analysis and/or to patients' age (children, adolescents or adults) adherence may vary between 41 and 85%¹⁰⁻¹⁴. However, in all studies, poorer adherence was associated with more breakthrough bleeds and more target joint bleeds and, when identified, reduced quality of life^{1,9}.

Currently, the only validated questionnaire to assess adherence to prophylaxis in haemophilia patients is the VERITAS-Pro scale²⁴, though in some cases other methods have been used, for example: 1) surveys and interviews with parents or their children; 2) quantity of factor actually used compared with prescribed dosage; or 3) infusion log records and the prescribed dosage and infusion frequency^{13,25-27}. In our study, the level of adherence was defined as the percentage of factor concentrate administered compared to the amount of concentrate prescribed, as reported by Hacker *et al.*¹¹. Besides conducting a survey, we also verified the amount of concentrate used and other variables by following up the patient at the Haemophilia Treatment Centre (HTC) every 6 months for 3 years. Although all subjects are regularly followed, a clinical study allows clinicians to devote more time to making patients understand the importance of proper prophylaxis.

We prospectively confirmed levels of high adherence in all the haemophilia patients (children, adolescents and adults) on prophylaxis over the whole period of examination, as similarly observed in other non-prospective studies of European haemophilia patients¹³.

The number of bleeding episodes reported decreased during the period of observation and the number of patients free of any bleeding gradually rose from 50% at the beginning of the study to 72% three years later.

During the three years of study, there was a decrease in the number of school/work days lost in both groups. The percent reduction was higher in the adherent group (−94%) than in the non-adherent group (−67%). This indicates that, by the end of the study, the patients adhering to the therapy (who even before entering the study paid greater attention to the correct treatment of their disease) were losing almost no work/school days due to bleeding.

The reduction of target joints and an improved HJHS score during the prophylactic period of observation are also worthy of mention.

Highly adherent patients did more sport and engaged in more physical activities with a medium impact on joints compared to patients with no or low adherence. In our study, we found some differences between adolescents and adults in the type, frequency, and impact of physical activity. The patients who had better orthopaedic joint scores reported better subjective physical performance.

The number of non-adherent patients was too low to allow an adequate statistical comparative analysis with adherent patients. Moreover, the total number of patients enrolled was limited, but the study followed all the patients prospectively for up to three years and data on adherence were calculated over a long-term observation period. The data obtained refer to a recombinant single product and this has to be taken into account, since adherence might vary if other products

are prescribed (e.g. due to differences in reconstitution process). Comparative studies are needed to confirm or refute our results.

However, the study has the merit of being the first prospective study which correlates adherence to prophylaxis with physical activity in haemophiliacs.

Conclusions

The results of this study showed high adherence to prophylaxis in our Italian population of haemophilia A patients, and this correlated with a significant reduction in bleeding events, number of target joints, and school/work days lost over time, and a steady improvement in performance during endurance sports activities.

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