Journal of Blood Medicine

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ORIGINAL RESEARCH

The Impact of Pharmacokinetic-Guided Prophylaxis on Clinical Outcomes and Healthcare Resource Utilization in Hemophilia A Patients: Real-World Evidence from the CHESS II Study

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Background: Using a pharmacokinetic (PK)-guided approach to personalize the dose and frequency of prophylactic treatment can help achieve and maintain targeted factor VIII (FVIII) trough levels in patients with hemophilia A.

Objective: Investigate clinical and healthcare resource use outcomes in patients with hemophilia A treated with or without PK-guided prophylaxis using data from the Cost of Haemophilia in Europe: A Socioeconomic Survey (CHESS) II database.

Methods: CHESS II was a cross-sectional, retrospective, burden-of-illness study incorporating data from eight European countries. Patients were eligible for this analysis if they were male, ≥18 years of age, and diagnosed with congenital hemophilia A of any severity. The clinical endpoints included annualized bleeding rate (ABR), presence and number of problem/target joints, and occurrence of joint surgeries. Healthcare resource utilization endpoints included the number of hematologist consultations and bleed-related hospitalizations or emergency department admissions. Data from November 2018 to October 2020 were included and were stratified according to treatment regimen and use of PK-guided dosing.

Results: Altogether, 281 patients on prophylaxis had available FVIII trough level data. Mean (SD) age was 35.7 (13.8) years. A specific FVIII trough level was targeted in 120 (42.7%) patients and 47 (39.2%) received PK-guided dosing. Patients receiving PK-guided dosing had a mean (SD) ABR of 2.8 (2.1) and target joint number of 0.5 (0.7), compared with 3.9 (2.7) and 0.9 (1.4), respectively, for patients receiving non–PK-guided treatment. The mean (SD) number of hematologist consultations was 7.1 (5.3) for patients receiving PK-guided dosing versus 10.7 (5.7) for those who were not. A higher proportion of patients in the non–PK-guided group required hospitalization during their lifetime compared with the PK-guided group.

Conclusion: This analysis of real-world data suggests that PK-guided dosing for prophylaxis has a beneficial impact on clinical and healthcare resource utilization outcomes in patients with hemophilia A.

Keywords: hemophilia A, recombinant factor VIII, prophylaxis, PK-guided dosing, personalized treatment, CHESS II

Introduction

Hemophilia A is a congenital, recessive, X-linked disorder characterized by a deficiency or absence of clotting factor VIII (FVIII), leading to frequent, acute, and prolonged spontaneous or traumatic bleeding events.[1] The severity of hemophilia A is classified on the basis of FVIII levels as severe (<0.01 IU/mL), moderate (0.01–0.05 IU/mL), or mild (0.05–0.4 IU/mL).[1,2] Individuals with severe hemophilia A often experience hemophilic arthropathy due to joint bleeding, characterized by chronic inflammation and progressive joint deformity, leading to chronic pain, disability, and impaired quality of life.[2,3] Treatment for hemophilia includes replacement of FVIII through intravenous injections to achieve adequate hemostasis, or the use of agents to enhance hemostasis independently of factor replacement, such as with the bispecific antibody emicizumab, which mimics FVIII activity.[2,4–6] Patients can be treated with on-demand FVIII

Received: 23 February 2022
Accepted: 30 August 2022
Published: 19 September 2022

replacement, to stop a bleed that has already occurred or prophylactically.[5] The current standard of care for severe hemophilia A includes prophylaxis, involving 2–3 or more weekly intravenous injections with FVIII replacement therapy to keep FVIII levels above 1% in order to prevent bleeding episodes, target joint development, and resultant hemophilic arthropathy.[2]

The standard prophylactic treatment strategy was initially based on data demonstrating a significant reduction in bleeding frequency when FVIII levels of ≥1% were maintained.[7,8] However, although achieving a target FVIII trough level of 1% significantly reduces bleeding, some patients with hemophilia A still experience bleeding events, including into joints and soft tissue, leading to high morbidity.[1,8,9] In addition, the shorter half-life of standard half-life FVIII replacement therapies necessitates frequent infusions to maintain FVIII levels, which can be challenging for patients, resulting in suboptimal treatment adherence. Extended half-life (EHL) recombinant FVIII concentrates have been developed to address this need. Many approaches to FVIII prophylaxis exist, and there is no consensus on the optimal strategy for dosing and treatment frequency to reduce the number and intensity of bleeds in individual patients. The optimal FVIII target trough level depends on a patient's individual pharmacokinetic (PK) profile, lifestyle, hemorrhagic history, and joint health.

In order to further improve the current standard of care, the World Federation of Hemophilia guidelines now recommend using a more personalized and tailored prophylactic treatment approach in patients who do not have satisfactory outcomes with standard prophylaxis. This approach targets FVIII trough levels >3–5% on the basis of an individual's PK profile, bleeding pattern, and lifestyle.[2,10]

A number of studies have addressed the potential benefits of using PK profiling to personalize FVIII prophylaxis to help achieve and maintain a target trough level.[10–16] PK profiling has also been shown to have economic benefits compared with standard prophylaxis.[17,18] However, data from controlled clinical trials are limited, and information on the benefit of targeting higher FVIII trough levels has therefore been derived from a modeling approach.[19–23] The recent phase 3, prospective, randomized, open-label, multicenter PROPEL study (NCT02585960) evaluated the safety and efficacy of the EHL recombinant FVIII rurioctocog alfa pegol at two PK-guided target FVIII trough level ranges (1–3% and 8–12%). This study demonstrated that a higher proportion of patients achieved zero bleeds when an elevated FVIII trough level was targeted.[24]

However, despite more patients achieving a goal of zero bleeds, specifically in the group targeting a higher trough level, avoidable bleeds still occurred in both treatment groups.[7] This raises the question of what the ideal target trough level for optimized bleed protection is and suggests that there is a need to match the target trough to the individual patient's needs. Given the variability associated with the care of individual patients and their responses to FVIII treatment, clinicians must evaluate the various risk factors and estimate the personalized target trough level a patient requires for the prevention of bleeding. Personalizing FVIII prophylaxis to a patient's PK profile can serve as a useful tool to aid clinicians in decision-making.

There remains, however, a lack of real-world evidence to suggest optimal prophylactic treatment strategies and, specifically, the benefits of PK-guided dosing in comparison with standard prophylaxis on clinical outcomes and healthcare resource utilization. The aim of the current analysis was to describe and compare clinical outcomes and healthcare resource utilization between patients with hemophilia A treated with or without PK-guided dosing using data from the Cost of Haemophilia in Europe: A Socioeconomic Survey (CHESS) II database.

Methods

Study Design and Patient Population

CHESS II is a cross-sectional, 12-month, retrospective, prevalence-based, burden-of-illness study conducted across eight European countries (France, Germany, Italy, Spain, the UK, Denmark, the Netherlands, and Romania). The CHESS II study used the same methodology that was used for the previously published CHESS study.[25] Patients were eligible to participate in CHESS II if they were male, ≥18 years of age, had been diagnosed with non-acquired hemophilia A or B of any severity and were able to read, understand, and sign the informed consent form. Patient data were collected from two questionnaires: a physician-completed, web-based clinical record form and a corresponding paper-based patient self-completion questionnaire

(Patient and Public Involvement and Engagement [PPIE]). The clinical record form contained information about the patient's medical history and consultations, and the PPIE covered non-medical costs, health-related quality of life (via the EuroQol EQ-5D-5L), and work impairment (via the Work Productivity and Activity Impairment instrument).

The present retrospective analysis was conducted on data from patients with hemophilia A of any severity without inhibitors, with complete responses for the variables of interest from the interim CHESS II dataset. Data collected between November 2018 and October 2020 were analyzed.

All patient participants provided informed consent and the study protocol was approved by the Research Ethics Sub Committee of the Faculty of Health and Social care within the University of Chester. The approval stipulated that the study was to be carried out in correspondence with regional and relevant guidelines.

Analysis Endpoints

This retrospective analysis of the CHESS II dataset included primary clinical and healthcare resource utilization outcomes associated with the care of patients with hemophilia A. The primary clinical endpoints included annualized bleeding rate (ABR) for the 12-month observation period immediately preceding data collection, joint outcomes, and whether the patient had undergone joint surgery in the previous 12 months or during their lifetime. Joint outcomes were characterized as the presence and number of target joints and/or problem joints. A target joint is defined as a joint in which ≥3 spontaneous bleeds have occurred within a consecutive 6-month period. Where there have been ≤2 bleeds into the joint within a consecutive 12-month period, the joint is no longer considered a target joint.[26] A problem joint is defined as a joint affected by chronic pain and/or limited range of motion due to compromised joint integrity (ie, suffering from chronic synovitis, and/or hemophilic arthropathy), with or without recurrent bleeding.[27] Physician-reported adherence to the prophylaxis treatment regimen was also assessed and is reported as the proportion of patients who are fully adherent to their regimen (defined as missing <15% of infusions).

Healthcare resource utilization was also assessed across subgroups by analyzing the proportion of patients requiring specialist hematologist or nurse consultations and the number of specialist consultations needed in the 12 months prior to data collection. Bleed-related hospitalizations and emergency department admissions were also assessed, including the type of hospitalization (ward, intensive care unit [ICU], day case), number of hospitalizations, and duration of hospital stay.

Statistical Analysis

Demographic data and outcomes of interest were reported descriptively and stratified according to subgroups defined by the treatment characteristics. Specifically, strata were defined by whether the patients received primary prophylaxis (ie, treatment has always been prophylactic with regular factor infusions to prevent bleeding commencing before significant bleeding has occurred) or secondary prophylaxis (treatment was previously on demand but, after experiencing several bleeds into a target joint, the patient is now receiving regular prophylactic infusions). Among those for whom a FVIII trough level was targeted, data were also stratified by how the specific treatment dose was determined (ie, whether the dose was PK guided or not).

Univariate and multivariate regression analyses for bleeding outcomes were performed with continuous and categorical variables using ordinary least-squares regression (OLS). Models were specified for both subcohorts with information on dose-determination method (n = 120). Basic demographics and covariates that were clinically relevant or significantly associated with ABR and resource utilization outcomes ($p < 0.10$) were selected for multivariate analysis of the relationship of clinical attributes, treatment strategy and use of PK-guided dosing with bleeding and resource utilization outcomes (hospitalizations). Multicollinearity between covariates was assessed using Pearson's correlation coefficient (PCC) before inclusion in the regression model. The assumptions of normality of OLS were assessed via visual inspection of quantile–quantile plots and distribution of residuals. Robust standard errors were employed to account for heteroscedasticity.

Data analysis was undertaken using Stata Statistical Software: Release 16, 2019 (StataCorp, College Station, TX, USA). Imputation of missing data was not conducted. Patients with missing responses for the outcomes of interest were

excluded from the analysis. Continuous variables and study outcomes were summarized using non-missing sample size (n) and percentage of non-missing sample size and means and standard deviations (SD).

Results

Sample Characteristics

The dataset used in this analysis included 1337 patients treated by 185 hematologists and hemophilia care providers based in hospitals and clinics, and captured 366 PPIEs. Of these, 281 patients with hemophilia A receiving prophylaxis met the inclusion criteria and were included in this analysis. Patient demographics and characteristics are presented in Table 1. The

Table 1 Patient Demographics and Baseline Characteristics

Parameter	Secondary Prophylaxis	Primary Prophylaxis	PK-Guided	Non–PK-Guided	Full Sample
Total patients, N	128	153	47	73	281
Age, years					
Mean ± SD	38.3 ± 14.4	33.5 ± 12.9	38.4 ± 15.9	35.3 ± 14.0	35.7 ± 13.8
Median (range)	38 (19–79)	29 (18–77)	32 (18–79)	29 (19–75)	32 (18–79)
Country, n (%)					
Italy	54 (42.2)	33 (21.6)	15 (31.9)	20 (27.4)	87 (31.0)
Spain	36 (28.1)	24 (15.7)	8 (17.0)	28 (38.4)	60 (21.4)
UK	12 (9.4)	43 (28.1)	7 (14.9)	2 (2.7)	55 (19.6)
Germany	7 (5.5)	42 (27.5)	10 (21.3)	10 (13.7)	49 (17.4)
France	19 (14.8)	11 (7.2)	7 (14.9)	13 (17.8)	30 (10.7)
Ethnicity, n (%)					
White	118 (92.2)	144 (94.1)	46 (97.9)	67 (91.8)	262 (93.2)
Asian-other	2 (1.6)	3 (2.0)	0	0	5 (1.8)
Mixed	4 (3.1)	1 (0.7)	0	2 (2.7)	5 (1.8)
Black/Afro-Caribbean	2 (1.6)	2 (1.3)	0	0	4 (1.4)
Middle Eastern	1 (0.8)	2 (1.3)	0	2 (2.7)	3 (1.1)
Asian-Indian subcontinent	0	1 (0.8)	1 (2.1)	2 (2.7)	1 (0.4)
Prefer not to answer	1 (0.8)	0	0	0	1 (0.4)
Body mass index, kg/m^2, mean ± SD	24.9 ± 2.7	24.5 ± 2.9	24.8 ± 2.3	24.1 ± 2.6	24.7 ± 2.8
Weight, kg, mean ± SD	74.2 ± 9.3	75.9 ± 10.1	75.6 ± 9.2	73.3 ± 9.7	75.1 ± 9.8
Physician targeting a specific FVIII trough level for the patient[a], n (%)					
Yes	61 (47.7)	59 (38.6)	47 (100)	0	120 (42.7)
No	67 (52.3)	94 (61.4)	0	73 (100)	161 (57.3)
Dosage guided by PK profiling, n (%)					
Yes	17 (27.9)	30 (50.8)	47 (100)	0	47 (39.2)
No	44 (72.1)	29 (49.1)	0	73 (100)	73 (60.8)
Treatment type, n (%)					
Extended half-life	21 (16.4)	36 (23.5)	13 (27.7)	13 (17.8)	57 (20.3)
Standard half-life	107 (83.6)	117 (76.5)	34 (72.3)	60 (82.2)	224 (79.7)

Notes: [a]The specific FVIII trough levels targeted were recorded as part of this study; however, owing to the high levels of variation, these data were not included as part of this analysis.
Abbreviations: FVIII, factor VIII; PK, pharmacokinetic; SD, standard deviation.

mean (SD) patient age was 35.7 (13.8) years, and the mean (SD) patient body mass index was 24.7 (2.8) kg/m^2. All patients had severe hemophilia A (FVIII < 1%). Most patients were from Italy (87 [31.0%]) and Spain (60 [21.4%]), and >90% of patients were of White ethnicity (262 [93.2%]). No patients from Denmark, Romania, or the Netherlands were included owing to small sample sizes and failure to meet the inclusion criteria. Of the 281 included patients, 153 (54.4%) were receiving primary prophylaxis and 128 (45.6%) were receiving secondary prophylaxis. A specific FVIII trough level was targeted by the physician for 120 patients (42.7%) and, of those, treatment dosage was guided by PK profiling for 47 (39.2%). Although the specific FVIII trough levels targeted were recorded as part of the CHESS II study, because of the small sample size, these have not been included in the reported analysis. Use of EHL therapy was numerically more common in the primary prophylaxis group compared with the secondary prophylaxis group (23.5% vs 16.4%, respectively), and in patients receiving PK-guided therapy compared with non–PK-guided therapy (27.7% vs 17.8%, respectively).

Descriptive Analysis of Clinical Attributes and Treatment Characteristics

ABRs and Joint Deterioration

ABRs and joint health outcomes stratified by treatment groups are shown in Table 2. Patients receiving primary prophylaxis exhibited a numerically lower mean (SD) ABR than patients receiving secondary prophylaxis (2.9 [2.6] vs 4.0 [3.0], respectively; p = 0.001). In addition, only 27.5% of patients receiving primary prophylaxis had target joints, compared with 46.9% of the patients receiving secondary prophylaxis (p = 0.001). The proportions of patients with problem joints and the overall number of target joints and problem joints were similar between the two treatment strategy groups (Table 2). A numerically higher proportion of patients receiving secondary prophylaxis were found to be fully adherent compared with patients receiving primary prophylaxis (84.4% vs 77.1%, respectively) (Table 2).

Patients receiving PK-guided prophylaxis exhibited a lower ABR than patients in the non–PK-guided group (2.8 [2.1] vs 3.9 [2.7], respectively). Patients receiving PK-guided dosing also reported a slightly lower mean (SD) number of target joints compared with the non–PK-guided group (0.5 [0.7] vs 0.9 [1.4], respectively). However, a higher proportion of patients in the PK-guided group (51.1%) experienced problem joints compared with the non–PK-guided group (42.5%) (Table 2). The proportion of fully adherent patients was very similar between patients receiving PK-guided (78.1%) and non–PK-guided prophylaxis (78.7%) (Table 2).

Table 2 Bleeding Rates, Joint Deterioration, and Treatment Adherence Stratified by Treatment Group

	Treatment Strategy (N = 281)			**Targeting FVIII Trough Level (N = 120)**		
	Secondary Prophylaxis[d] (n = 128)	**Primary Prophylaxis[e] (n = 153)**	**p-value**	**PK-Guided (n = 47)**	**Non–PK-Guided (n = 73)**	**p-value**
ABR, mean ± SD	4.0 ± 3.0	2.9 ± 2.6	0.001	2.8 ± 2.1	3.9 ± 2.7	0.022
Presence of target joints[a], n (%)	60 (46.9)	42 (27.5)	0.001	18 (38.3)	30 (41.1)	0.760
Number of target joints[a], mean ± SD	0.8 ± 1.1	0.5 ± 1.0	0.058	0.5 ± 0.7	0.9 ± 1.4	0.036
Presence of problem joints[b], n (%)	59 (46.1)	64 (41.8)	0.473	24 (51.1)	31 (42.5)	0.356
Number of problem joints[b], mean ± SD	0.8 ± 1.0	0.7 ± 1.1	0.995	0.8 ± 0.9	0.8 ± 1.1	0.834
Fully adherent[c], n (%)	108 (84.4)	118 (77.1)	0.116	37 (78.7)	57 (78.1)	0.759

Notes: [a]A target joint was defined as a joint in which ≥3 spontaneous bleeds occurred within a consecutive 6-month period. The joint was no longer considered a target joint if the patient experienced ≤2 bleeds into the joint within a consecutive 12-month period. [b]A problem joint was defined as a joint exhibiting any symptoms among chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding. [c]Full adherence was reported by the physician and defined as "Missing <15% of infusions." [d]Secondary prophylaxis was defined as treatment that was previously on-demand but is currently prophylactic. [e]Primary prophylaxis was defined as treatment that has always been prophylactic.
Abbreviations: ABR, annualized bleeding rate; FVIII, factor VIII; PK, pharmacokinetic; SD, standard deviation.

Joint Surgeries

The number of patients who underwent joint surgery and the number of joint surgeries received, stratified by treatment group, are presented in Table 3. A higher proportion of patients receiving primary prophylaxis underwent joint surgery during the 12 months prior to data collection compared with those receiving secondary prophylaxis (60.5% vs 45.2%, respectively). However, the mean (SD) number of surgeries performed per patient was 1.7 (1.1) for patients receiving primary prophylaxis, compared with 2.4 (1.6) for the secondary prophylaxis group (Table 3).

A higher proportion of patients receiving PK-guided prophylaxis also underwent joint surgeries in their lifetime compared with those receiving non–PK-guided prophylaxis (29.8% vs 24.7%). However, a lower proportion of patients in the PK-guided group underwent a joint surgery in the 12 months immediately prior to data collection (50.0% vs 83.3%), with only two patients (4.3%) undergoing ≥3 joint surgeries in the prior 12 months. The mean (SD) number of surgical procedures in the 12 months prior to data collection was also slightly lower in patients receiving PK-guided prophylaxis (2.1 [1.3] vs 2.7 [1.5]) (Table 3).

Healthcare Resource Utilization

Specialist consultations, including the number of scheduled and unscheduled visits, stratified by treatment group are presented in Table 4. Patients receiving primary prophylaxis reported a similar mean (SD) number of specialist hematologist visits (7.8 [5.6]) to those who received secondary prophylaxis (8.0 [5.3]). However, patients receiving primary prophylaxis reported a lower mean (SD) number of specialist nurse visits (6.5 [6.1] vs 7.9 [9.5]).

Patients whose dosing was PK guided reported a lower mean (SD) number of hematologist and nurse consultations (7.1 [5.3] and 5.2 [4.2], respectively) than patients receiving non–PK-guided dosing (10.7 [5.7] and 10.3 [11.7], respectively). Additionally, patients receiving PK-guided dosing reported fewer unscheduled specialist consultations (hematologist consultations = 1.9 [4.4] vs 2.3 [2.5]; nurse consultations = 1.2 [1.7] vs 2.3 [3.2]) (Table 4).

The proportions of patients requiring bleed-related hospitalization in their lifetime and during the 12 months immediately prior to data collection, as well as the number and type of hospitalizations stratified by treatment group,

Table 3 Joint Surgeries Stratified by Treatment Group

	Treatment Strategy (N = 281)		**Targeting FVIII Trough Level (N = 120)**	
	Secondary Prophylaxis[c] (n = 128)	**Primary Prophylaxis[d] (n = 153)**	**PK-Guided (n = 47)**	**Non–PK-Guided (n = 73)**
Patients who underwent joint surgery in their lifetime, n (%)	32 (25.0)	38 (24.8)	14 (29.8)	18 (24.7)
Patients who underwent joint surgery in the 12 months prior to data collection, n (%)	16 (50.0)	22 (57.9)	7 (50.0)	15 (83.3)
Number of joint surgeries in the 12 months prior to data collection, n (%)				
0 1 2 ≥3	112 (87.5) 6 (4.7) 4 (3.1) 6 (4.7)	131 (85.6) 11 (7.2) 7 (4.6) 4 (2.6)	40 (85.1) 3 (6.4) 2 (4.3) 2 (4.3)	58 (79.5) 4 (5.5) 3 (4.1) 8 (11.0)
Total number of surgical procedures on target[a] and problem[b] joints in the 12 months prior to data collection, mean ± SD (n = 37)	2.4 ± 1.6 (n = 14)	1.7 ± 1.1 (n = 23)	2.1 ± 1.3 (n = 7)	2.7 ± 1.5 (n = 15)

Notes: [a]A target joint was defined as a joint in which ≥3 spontaneous bleeds occurred within a consecutive 6-month period. The joint was no longer considered a target joint if the patient experienced ≤2 bleeds into the joint within a consecutive 12-month period. [b]A problem joint was defined as a joint exhibiting any symptoms among chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding. [c]Secondary prophylaxis was defined as treatment that was previously on demand but is currently prophylactic. [d]Primary prophylaxis was defined as treatment that has always been prophylactic.
Abbreviations: FVIII, factor VIII; PK, pharmacokinetic; SD, standard deviation.

Table 4 Healthcare Resource Utilization Stratified by Treatment Group

	Treatment Strategy (N = 281)		Targeting FVIII Trough Level (N = 120)	
	Secondary Prophylaxis[a] (n = 128)	Primary Prophylaxis[b] (n = 153)	PK-Guided (n = 47)	Non–PK-Guided (n = 73)
Number of hematologist consultations, mean ± SD	8.0 ± 5.3	7.8 ± 5.6	7.1 ± 5.3	10.7 ± 5.7
Number of scheduled hematologist consultations	6.2 ± 4.0	6.1 ± 3.9	5.2 ± 3.0	8.4 ± 4.2
Number of unscheduled hematologist consultations	1.8 ± 2.1	1.8 ± 3.2	1.9 ± 4.4	2.3 ± 2.5
Number of nurse consultations, mean ± SD	7.9 ± 9.5	6.5 ± 6.1	5.2 ± 4.2	10.3 ± 11.7
Number of scheduled nurse consultations	5.9 ± 7.6	5.1 ± 5.0	4.0 ± 3.3	8.0 ± 9.4
Number of unscheduled nurse consultations	2.0 ± 2.8	1.5 ± 2.3	1.2 ± 1.7	2.3 ± 3.2

Notes: [a]Secondary prophylaxis was defined as treatment that was previously on demand but is currently prophylactic. [b]Primary prophylaxis was defined as treatment that has always been prophylactic.
Abbreviations: FVIII, factor VIII; PK, pharmacokinetic; SD, standard deviation.

are shown in Table 5. A higher proportion of patients receiving secondary prophylaxis were hospitalized within the 12 months prior to data collection (62.6%) compared with patients receiving primary prophylaxis (86.4%).

The proportion of patients requiring hospitalization during their lifetime was also lower for those receiving PK-guided dosing (80.9%) than for those receiving non–PK-guided dosing (90.4%). Patients receiving PK-guided dosing were also observed to have experienced fewer ward hospitalizations during the 12 months prior to data collection than those receiving non–PK-guided dosing, with mean (SD) numbers of hospitalizations of 0.4 (0.8) and 0.6 (1.0), respectively.

Regression Analysis

Table 6 summarizes the univariate regression analysis. Variables of clinical relevance and those demonstrating a significant association with the outcome of interest were included in the multivariate analysis.

Table 5 Bleed-Related Hospitalizations Stratified by Treatment Group

	Treatment Strategy (N = 281)		Targeting FVIII Trough Level (N = 120)	
	Secondary Prophylaxis[b] (n = 128)	Primary Prophylaxis[c] (n = 153)	PK-Guided (n = 47)	Non–PK-Guided (n = 73)
Patients requiring hospitalization during their lifetime, n (%)	107 (83.6)	132 (86.3)	38 (80.9)	66 (90.4)
Patients requiring hospitalization in the 12 months prior to data collection, n (%)	67 (62.6)	114 (86.4)	33 (86.8)	44 (66.7)
Hospitalizations occurring in the 12 months prior to data collection, mean ± SD				
Number of ward hospitalizations	0.5 ± 0.9	0.5 ± 0.9	0.4 ± 0.8	0.6 ± 1.0
Number of days on ward	5.7 ± 4.2 (n = 51)	6.9 ± 5.1 (n = 44)	8.4 ± 6.9 (n = 14)	5.7 ± 4.1 (n = 27)
Number of day cases[a]	0.1 ± 0.3	0.1 ± 0.6	0.1 ± 0.4	0.1 ± 0.3
Number of day-case days	1.0 ± 0.0 (n = 9)	2.3 ± 1.5 (n = 8)	1.5 ± 0.6 (n = 4)	1.3 ± 0.6 (n = 3)
Number of ICU hospitalizations	0.1 ± 0.3	0.1 ± 0.3	0.1 ± 0.2	0.6 ± 1.0
Number of days in ICU	2.7 ± 1.3 (n = 12)	2.3 ± 1.1 (n = 7)	1.7 ± 1.2 (n = 3)	1.5 ± 0.6 (n = 4)

Notes: [a]A day case was defined as a patient who visited hospital but did not stay overnight. [b]Secondary prophylaxis was defined as treatment that was previously on demand but is currently prophylactic. [c]Primary prophylaxis was defined as treatment that has always been prophylactic.
Abbreviations: FVIII, factor VIII; ICU, intensive care unit; PK, pharmacokinetic; SD, standard deviation.

Table 6 Multivariate Regression Results – Covariate Relationships with ABR and Hospitalizations

Variable	Relationship with Bleeding Rate		Relationship with Hospitalization Number	
	B-coefficient	**95% Confidence Interval**	**B-coefficient**	**95% Confidence Interval**
BMI	–0.007	–0.214, 0.199	0.017	–0.053, 0.088
Age group				
18–25	Reference	–	Reference	–
26–35	0.029	–1.022, 1.080	–0.159	–0.530, 0.211
36–50	–0.097	–1.486, 1.292	–0.107	–0.601, 0.386
51+	0.465	–1.212, 2.142	–0.436	–1.000, 0.127
Country[a]				
Germany	Reference	–	–	–
Spain	1.627	0.101–3.153	0.244	–0.431, 0.920
France	0.504	–0.652, 1.660	–0.314	–0.823, 0.195
Italy	1.218	–0.178, 2.614	–0.085	–0.781, 0.612
UK	1.496	0.265–2.727	–0.006	–1.055, 1.042
PK-guided dosing use	–0.903**	–1.790, –0.016	0.114	–0.169, 0.397
ABR	NA	NA	0.198***	0.125–0.272
Problem joint number	0.563**	0.037–1.090	0.240***	0.062–0.418
Full adherence[b]	–	–	–0.574**	–1.062, –0.085
Treatment type (EHL)	1.407**	0.161–2.653	–0.623**	–1.122, –0.124
Treatment strategy				
Primary prophylaxis	Reference	–	Reference	–
Secondary prophylaxis	–0.718	–1.829, 0.393	0.068	–0.266, 0.403

Notes: [a]No patients from Denmark, Romania, or the Netherlands were included owing to small sample sizes and failure to meet the inclusion criteria. [b]There was no significant relationship with ABR in the univariate analysis (p=0.43). **p<0.05; ***p<0.01.
Abbreviations: ABR, annualized bleeding rate; BMI, body mass index; EHL, extended half-life; NA, not applicable; PK, pharmacokinetics.

Bleeding Outcomes

The multivariate regression of data from the PK subsample results suggest that ABR is higher in patients from Spain and the UK compared with those from Germany ($p < 0.05$ for both; Table 6). Presence and increasing number of problem joints were found to be a significant driver of bleeding outcomes (both $p < 0.05$; Table 6). However, use of EHL FVIII concentrates had a positive and significant relationship with ABR ($p < 0.05$), despite demonstrating a weak correlation with the bleeding outcome itself (PCC = –0.03; $p = 0.74$). After controlling for treatment history and body mass index, use of PK-guided dosing was negatively associated with bleeding outcomes ($p < 0.05$; Table 6).

Hospitalizations

In this multivariate model, the aggregate number of hospitalizations (ie, the sum of all types of hospitalizations) was used as the dependent variable. ABR and number of problem joints were both identified as positively and significantly associated with number of hospitalizations ($p < 0.001$ and $p < 0.01$, respectively; Table 6). Fewer hospitalizations were experienced by fully adherent patients compared with non-fully adherent patients ($p < 0.05$; Table 6). The use of PK-guided dosing showed a positive association with number of hospitalizations, although this was not statistically significant ($p = 0.426$).

Discussion

The objective of this analysis of the CHESS II dataset was the investigation of relevant patterns in clinical or resource utilization outcomes across different treatment strategies and dosing approaches in the real world. This will generate relevant examples and assist stakeholders in the determination of the best-suited approach for managing patients with hemophilia A. The impact of a prophylactic treatment regimen guided by PK profiling was compared with a regimen without PK-guided dosing. Patients who were treated with primary prophylaxis appeared to have lower ABRs and a lower likelihood of experiencing target joints than patients treated with secondary prophylaxis. Importantly, ABR is the main outcome in hemophilia as bleeding is the source of all other complications. A reduction in ABR is therefore important in achieving better joint health in the longer term. Patients receiving primary prophylaxis did, however, have a slightly higher incidence of joint surgery in the 12 months before data collection compared with patients receiving secondary prophylaxis (58% vs 50%). In addition, patients whose prophylactic dose and regimen was guided by PK profiling had a lower ABR (2.8) than patients whose regimen was not PK guided (3.9). These ABRs are consistent with values presented for patients using PK-guided prophylaxis to target FVIII trough levels in the PROPEL study.[25] Short-term joint health outcomes were also more favorable for patients in the PK-guided group, with these patients experiencing fewer target joints and being less likely to have required joint surgery in the previous 12 months. This is despite the worse long-term joint health issues characterizing the patients belonging to the PK-guided group, inferred from the larger proportion of patients with existing problem joints and who had undergone joint surgeries in their lifetime when compared with the patients in the non–PK-guided group. Additionally, a slightly larger proportion of the non–PK-guided group of patients underwent >3 surgeries in the 12 months prior to data collection.

Specialist consultations were common across the groups, with patients receiving secondary prophylaxis requiring a higher number of nurse consultations than those treated with primary prophylaxis. Interestingly, of the patients receiving targeted treatment, those whose dosage was PK guided required fewer hematologist consultations (7.1 vs 10.7) and fewer nurse consultations (5.2 vs 10.3) than patients whose dosage was not PK guided. In addition, patients in the non–PK-guided group were more likely to require an unscheduled consultation than patients receiving PK-guided dosage.

In the regression analysis of data from the PK subsample, ABRs were higher in patients from Spain and the UK than in those from Germany (the reference population). In addition, the presence and number of problem joints were a significant driver of bleeding outcomes. In the analysis of hospitalizations, higher ABR and number of problem joints were significantly associated with increased number of hospitalizations, while full adherence to therapy was associated with fewer hospitalizations.

EHL FVIII use was positively and significantly related to increased bleeding, which was unexpected given the theoretical improved protection provided by these agents compared with standard half-life products. This can be explained if, as seems probable, patients with more extensive joint damage and pain are more likely to receive EHL products than those with less severe disease. In the more severe patients, the existing joint damage may exacerbate bleeding outcomes despite EHL FVIII treatment. It should also be noted, however, that few patients in the analysis received EHL products, which may have skewed the results.

These data suggest that tailoring treatment using a PK-guided approach to target a specific FVIII trough level is associated with reduced bleeding and improved joint outcomes. This improvement in joint health occurred even though the patients receiving PK-guided prophylaxis had evidence of long-standing chronic joint damage, as can be inferred from the larger proportion of patients with existing problem joints and joint surgeries in their lifetime.

Additionally, the data presented here showing an association between ABR and PK-guided prophylaxis suggest that PK-guided prophylaxis may be connected with a reduced need for specialist consultations and fewer unscheduled consultations as a result of its proposed relationship with reduced bleeding. Due to the debate currently surrounding the most appropriate FVIII trough level to target in patients with hemophilia A, further real-world data are needed to investigate the use of PK profiling and how it can be used to provide a more accurate determination of the optimal target

FVIII trough range. This will aid our understanding of the benefit that personalized care can bring to patients and the entire healthcare system.

This analysis should be considered in the context of some limitations. This study was a secondary analysis of data from the existing CHESS II dataset. Therefore, the data were not collected for the specific purpose of this analysis. Because of the voluntary and retrospective nature of the participation of patients and physicians in the original CHESS II study, neither a degree of selection or recall bias nor errors in the transfer of data from the medical charts can be ruled out. Only a small sample of the hemophilia A population is represented, and information on the endpoints of interest was available for a limited number of patients. Given the small sample sizes, the outputs from this analysis should be interpreted with caution.

Conclusions

This analysis is an initial contribution to the investigation around determining the real-world impact that PK-guided prophylaxis may have on clinical and healthcare resource utilization outcomes in patients with hemophilia A. Primary prophylaxis and PK-guided prophylaxis seem to be associated with a reduced need for specialist consultations. In addition, reduced bleeding, improved joint health outcomes, and a reduced need for joint surgeries were observed in patients receiving PK-guided prophylaxis. In this cohort, PK-guided therapy was started when considerable damage was already present, suggesting that some patients receive less than optimal treatment until symptoms become substantial. The relationship of PK-guided therapy with reduced bleeding suggests that earlier initiation of PK-guided therapy may help preserve joint health. Further research is warranted to explore the specific FVIII trough levels targeted, as well as other potential drivers in the differences in clinical and healthcare resource utilization outcomes among patients who receive PK-guided prophylaxis.

Abbreviations

ABR, annualized bleeding rate; CHESS, Cost of Haemophilia in Europe: A Socioeconomic Survey; EHL, extended half-life; FVIII, factor VIII; ICU, intensive care unit; OLS, ordinary least-squares regression; PCC, Pearson's correlation coefficient; PK, pharmacokinetic; PPIE, Patient and Public Involvement and Engagement; SD, standard deviation.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are held under license by the University of Chester and are not publicly available. Upon reasonable request, and subject to review, the corresponding author will provide the analyses that support the findings of this research. Subject to certain criteria, conditions, and exceptions, access to the related data for researchers who provide a methodologically sound proposal may be considered by data owners HCD Economics and the University of Chester. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

Ethics Approval and Informed Consent

All patient participants provided informed consent and the study protocol was approved by the Research Ethics Sub Committee of the Faculty of Health and Social care within the University of Chester. The approval stipulated that the study was to be carried out in correspondence with regional and relevant guidelines.

Acknowledgments

Under the direction of the authors, medical writing and editorial support was provided by Laura Harrison, PhD, of Excel Medical Affairs (Fairfield, CT, USA) and was funded by Takeda Development Center Americas, Inc., Lexington, MA, USA. The abstract of this paper was presented at ISTH 2021 as a poster presentation with interim findings. The poster's abstract was published in Special Issue: Abstracts of the ISTH 2021 Virtual Congress of the International Society of Thrombosis and Haemostasis, July 17–21, 2021 in *Research and Practice in Thrombosis and Haemostasis*: https://onlinelibrary.wiley.com/doi/10.1002/rth2.12589.

Author Contributions

All authors contributed to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by Takeda Development Center Americas, Inc., Lexington, MA, USA. Takeda were involved in study conception, design, and interpretation of results, as well as drafting and submission of the manuscript.

Disclosure

EFG, TB, and JOH are employees of HCD Economics. SXS is an employee of Takeda Development Center Americas, Inc. The authors report no other conflicts of interest in this work.

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