Received: 16 September 2021 | Revised: 20 December 2021 | Accepted: 29 December 2021

DOI: 10.1111/hae.14489

Haemophilia WILEY

ORIGINAL ARTICLE

Clinical outcome and adherence rate in Scandinavian patients with intermediate-intensity prophylaxis before and after the switch of standard half-life FVIII products to BAY 81–8973

Alexandros Arvanitakis[1,2] | **Pål Andre Holme**[3,4] | **Erik Berntorp**[1] | **Jan Astermark**[1,2]

[1] Department of Translational Medicine, Lund University, Malmö, Sweden

[2] Department of Haematology, Oncology and Radiation Physics, Skåne University Hospital, Malmö, Sweden

[3] Department of Haematology, Oslo University Hospital, Oslo, Norway

[4] Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Correspondence
Alexandros Arvanitakis, Department of Translational Medicine, Lund University and Department of Haematology, Oncology and Radiation Physics, Skåne University Hospital, Malmö SE-205 02c, Sweden.
Email: alexandros.arvanitakis@med.lu.se

Funding information
Bayer Health Care

Abstract

Introduction: Treatment optimization in haemophilia A can be achieved by choice of FVIII product and knowledge of pharmacokinetics (PK), phenotype and adherence. A favourable PK profile of BAY 81–8973 (octocog alfa) (Kovaltry, Bayer AB) compared to other standard half-life (SHL) FVIII products has been suggested.

Aim: To evaluate whether the switch to BAY 81–8973, using the same dosing schedule, impact factor consumption and bleed rates, taking arthropathy and adherence into account

Methods: Forty patients on prophylaxis with SHL (median age 40.5 years) attending the haemophilia treatment centres in Malmö and Oslo were enrolled. The annualised bleeding rate (ABR) and joint bleeding rate (AJBR) before and after the switch to BAY 81–8973 was calculated. PK analyses were performed with WAPPS-Hemo. Joint health status and treatment adherence were assessed.

Results: The median ABR and AJBR was 0 before and after the switch, at both centres. The median yearly factor consumption was 3,345 IU/Kg/year in the entire study group corresponding to intermediate-intensity prophylaxis in most patients and with significantly more used in Malmö (3,862 IU/Kg/year), compared to Oslo (2,337 IU/Kg/year) (*P* .006). There was no correlation between arthropathy and bleeding. The median BAY 81–8973 t½ was 20 h (range 7.5–29 h), with significant correlation to VWF levels, and 13.4 h after exclusion of VWF outliers. Adherence to treatment was 97%.

Conclusions: Concentrate switch, using mainly intermediate-intensity regimens with high adherence rates, preserves excellent prophylaxis outcome using standard half-life FVIII products, indicating the value of individualized prophylaxis and close follow-up.

KEYWORDS
BAY 81—8973, haemophilia, Kovaltry, Octocog alfa, population pharmacokinetics, WAPPS-Hemo

1 | INTRODUCTION

Haemophilia A (HA) is caused by the deficiency or absence of factor VIII (FVIII) and characterized by bleeding diathesis, with joint bleeding as clinical hallmark.[1,2] Prophylactic replacement therapy in HA aims to reduce the risk of bleeding by raising FVIII levels,[1,2] thus preventing the development of haemophilic arthropathy.[3] Different FVIII products, with distinct manufacturing methods,[4,5] molecular[6] and pharmacokinetic[7] properties, have been used in the treatment of HA. BAY 81–8973 (octocog alfa, Kovaltry, Bayer AB) is a standard half-life (SHL) recombinant FVIII product,[8] with a suggested favourable pharmacokinetic profile compared to octocog alfa (Kogenate, Bayer AB and Advate, Takeda Pharma).[9,10] Interpersonal variability in factor VIII pharmacokinetics influences; however, the FVIII levels post-infusion and the outcome of treatment.[11] Population PK models, such as the Web-Accessible Population Pharmacokinetic service – Haemophilia (WAPPS-Hemo)[12] take this into account in a multivariable model of a relevant patient population, while requiring minimal sampling when compared to a conventional PK analysis.[13,14] This can help optimize treatment[15,16] and illuminate differences in the pharmacokinetic profiles of specific FVIII products.

Haemophilic arthropathy is the result of repeated hemarthroses, mainly affects the knee, elbow and ankle joints,[17,18] and can reduce quality of life.[19] The chronic synovitis and vascular fragility in haemophilic arthropathy can both predispose to bleeding and mimic its symptoms.[20] Furthermore, independent of the treatment regimen used, adherence to the prescribed treatment is essential for its effectiveness. Poor adherence is associated with more self-reported bleeding episodes for adults and days off school for children.[21]

Historically, significant differences in the clinical management of HA patients have existed between the Scandinavian countries. For example, whereas prophylaxis has been standard of care in Sweden since the 1970s, it became available in Norway during the 1990s.[22] However, haemophilia management in Scandinavia has since been harmonized, with the development of Nordic guidelines.[23,24]The aim of this study was to study and compare whether the switch between SHL products with slightly different PK properties with the same dosing schedule, have influenced the clinical outcome in terms of factor consumption and bleeds of patients attending two of the larger Scandinavian Haemophilia centres taking arthropathy and adherence into account.[25]

2 | METHODS

2.1 | Study design

This is an open label, non-interventional, single arm double-centre study, enrolling male patients above 12 years of age with moderate (FVIII:C 1–5 IU/dl) and severe HA (FVIII:C < 1 IU/dl), who had switched or were planned to switch to BAY 81–8973 from another SHL FVIII product. The patients had prophylaxis for more than 50 exposure days, had their previous FVIII product for at least 30 days prior to switching to BAY 81–8973, and no current inhibitor, as measured by the Nijmegen-modified Bethesda assay. Patients fulfilling the inclusion criteria were eligible. PK analysis with WAPPS-HEMO was performed on a subset of patients from the Malmö cohort to evaluate the pharmacokinetics of BAY 81–8973 and phenotype changes after the switch. The study was conducted between March 2017 and February 2020.

2.2 | Clinical data

Clinical data regarding age, height, weight, bleeds, and joint bleeds were collected. The bleeding events prior the switch to BAY 81–8973 were documented retrospectively the year preceding the study visit with a median duration of 12.5 months (IQR 10–13 months), after which the switch to BAY 81–8973 occurred. The bleeding events after the switch to BAY 81–8973 were documented for the period after the switch and prior the final study visit. The recording of bleeds was paper based after oral or written report from the patient or his caregiver. The annual bleeding rate (ABR) and annual joint bleeding rate (AJBR) were defined as the number of reported bleeding episodes and joint bleeding episodes divided by the observation period in months multiplied by 12. A target joint was defined as > 3 bleeding episodes in the same joint during 6 months. Joint health was assessed by the physiotherapist at the haemophilia centre according to the Haemophilia Joint Health Score (HJHS) version 2.1.[26] A cut off score 10 was applied to dichotomize the results between arthropathy and non-arthropathy, as used in previous studies.[27,28]

Adherence to therapy was measured with the validated VERITAS-PRO questionnaire[29] and filled out by the patient or their caregiver.[29] A cut-off score 57 defined non-adherence, as in previous studies.[29,30]

2.3 | FVIII and VWF: Ag assays and pharmacokinetic analysis

PK analysis was performed in 14 patients with severe HA, who were treated at the Coagulation Centre in Malmö. Analysis was based on two sparse samples collected at least 12 h apart, with no wash-out, between four and 48 h after BAY 81–8973 infusion, according to the ISTH guidelines.[31] FVIII levels with use of the chromogenic assay and VWF:Antigen (VWF:Ag) levels were estimated at the coagulation laboratory at Labmedicin Skåne according to local routines.

The WAPPS-HEMO web-based algorithm was used for population PK analysis. For the PK assessments, baseline FVIII activity, age, body weight, height, timing of the last two administered doses and infused dose were collected. The dosing regimen for each patient was at the discretion of the treating physician. The first sample was collected 4—8 h and the second sample 20–30 h post-infusion, respectively (Table 1).

2.4 | Statistical analysis

Descriptive statistics in the form of mean, median and interquartile ranges (IQR 25^{th}–75^{th} percentile) described continuous variables.

TABLE 1 Sampling time in hours post infusion for each patient and the corresponding FVIII levels measured by the chromogenic method at each time point

	Sample1		Sample 2		WAPPS-HEMO PK Estimations		
PAT-ID	Time (hrs post infusion)	FVIII level (%)	Time (hrs post infusion)	FVIII level (%)	t1/2 (hrs)	Time to 1% (hrs)	VWF:Ag (IU/dl)
1	5	63	23	31	24.0	159.8	193
3	5	41	25	11	13.5	85.5	MD
5	4	58	28	10	13.3	87.5	94
6	5	38	29	2	7.5	47.0	50
7	4	65	29	17	16.0	108.0	77
8	5	76	29	23	21.3	143.3	171
9	5	24	26	6	14.3	75.0	95
11	7	35	28	11	18.0	105.5	131
13	4	87	25	35	21.5	150.8	92
14	6	19	24	6	11.5	63.5	85
15	4	60	27	23	20.0	133.0	150
16	5	51	29	20	29.0	173.0	170
17	4	33	24	5	11.5	64.0	51
18	5	59	26	9	11.3	74.5	65

Calculated t1/2, time to troughs of 1% by WAPPS-Hemo, and VWF:Ag level at the sampling time for each patient are provided.
Abbreviations: VFW:Ag, Von Willebrand Factor antigen; PK, pharmacokinetic; hrs, hours; MD, missing data.

Statistical tests used were the Wilcoxon signed rank test, Mann-Whitney U test, Fischer's exact test and Spearman's correlation. All tests were performed using SPSS software, version 25 (IBM, Chicago, IL, USA). A *P*-value of $< .05$ was considered statistically significant.

2.5 | Ethics

The study was approved by the Regional Ethics Review Board of Lund University, Lund, Sweden and Oslo University, Oslo, Norway. The study subject or his legal representative provided written informed consent before entering the study.

3 | RESULTS

3.1 | Patient and treatment characteristics

Forty-three patients were enrolled corresponding to all patients who switched to BAY 81–8973 prophylaxis at the Malmö centre and one half of those in Oslo. One patient withdrew the day after inclusion for personal reasons and in one patient there was inadequate bleeding data. A third patient was excluded since he had been treated with extended half-life product efmoroctocog alfa (Elocta, Sobi), prior the switch to BAY 81–8973. Consequently, the final analysis included 40 patients (baseline clinical characteristics and demographics shown in Table S1), 18 patients treated at the Haemophilia centre in Malmö (#1-#18) and 22 patients treated at the Haemophilia centre in Oslo (#19-#40). All patients had severe Haemophilia A, except two patients who had moderate HA (#33 and #39 with baseline FVIII:C of 3 IU/dl and 2 IU/dl, respectively). There was no history of previous or current FVIII inhibitor. The type of SHL FVIII used prior to the switch to BAY 81–8973 was Kogenate in 21 patients, Helixate in 13, Advate in 5 pat and Refacto (moroctocog alfa, Pfizer) in 1. The median age of the entire cohort was 40.5 years (IQR 26.0–48.8) and the median BMI was 27.3 (IQR 23.4–30.4). The corresponding figures for the Malmö cohort were 35 years (IQR 20.5–44) with median BMI 26.9 (IQR 22.1–28.9) and for the severe HA patients of the Oslo cohort 44 years (IQR 34–56), with median BMI 25.3 (IQR 24.5–31.5). The median dose of infused FVIII before the switch was 20.4 IU/kg (IQR 12.9–26.2) and all patients received regular prophylaxis, either daily ($N = 4$), every other day ($N = 14$), three times weekly ($N = 14$) or two times weekly ($N = 6$). Two patients had a sparse infusion schedule of once weekly or less. All patients continued with the same dose and infusion frequency after the switch to BAY 81–8973, except for two patients (#19 and #26), whose infusion frequency was increased slightly, from three times weekly to every other day (Table S1). Dosing and median yearly FVIII consumption was otherwise essentially the same in both cohorts prior and after the switch. The median FVIII consumption for the entire cohort on BAY 81–8973 was 3345 IU/Kg/year (IQR 1944–4463) (Table S2). There was a significant difference in yearly factor consumption of BAY 81–8973, between the severe HA patients in the Malmö and Oslo cohort. The median FVIII dose per injection was 21.3 IU/Kg in Malmö (IQR 14.5–26.4), and the frequency of injections was 182 per year (IQR 156–227.8). The corresponding numbers in Oslo were 20 IU/Kg (IQR 12.2–25.1) and 156 (IQR 156–182), respectively. The Malmö cohort had median FVIII consumption of 3862 IU/Kg/year, compared to 2337 IU/Kg/year in the Oslo cohort (*P* .006)(Table 2).

TABLE 2 A comparison of clinical outcomes between the patients from Malmö ($n = 18$) and those from Oslo ($n = 20$) after the switch to BAY 81-8973

	Malmö ($N = 18$)		Oslo ($N = 20$)		
Parameter	Mean	Median (IQR)	Mean	Median (IQR)	*P*-value
ABR	.33	0 (0–0)	.42	0 (0–0)	.945
AJBR	.11	0 (0–0)	.26	0 (0–0)	.617
HJHS	17.7	9.5 (3–35)	17.1	14 (12–19.8)	.411
VERITAS-Pro	39.5	40 (28.5–47.5)	40.0	40 (31.8–46)	.885
FVIII Consumption (IU/Kg BW/Year	4,018	3,862 (3,174–4,860)	2,891	2,337 (1,843 –3,912)	.006

Abbreviations: ABR, annual bleeding rate; AJBR, annual joint bleeding rate; HJHS, Haemophilia Joint Health Score.

3.2 | Bleeding phenotype before and after the switch to BAY 81–8973

The median ABR was 0 (IQR 0–1.5) before and remained 0 (IQR 0–0) after the switch to BAY 81–8973. The corresponding median AJBR was 0 (IQR 0–0), both before and after the switch (Figure 1, Table S1). The mean ABR was 1.1 prior and .4 after the switch (*P* .136) and the mean AJBR .7 prior versus .3 after (*P* .194). The corresponding figures for the two subcohorts in Malmö and Oslo are shown on Table 2. Basically, the bleed rates are the same, although a slightly higher mean was observed for patients attending the Oslo centre.

Before the switch, 30 patients (75%) had an ABR of 0 and after the switch the corresponding number of patients was 33 (82.5%). The median ABR of the 10 patients with reported bleeds prior to the switch to BAY 81–8973 was reduced from 4 (IQR 0–6) to 0 (IQR 0–.25) (*P*. .007) and the median AJBR reduced from 2 (IQR 0–6) to 0 (IQR 0–0) (*P*. .017), respectively.

3.3 | Pharmacokinetic analysis of BAY 81–8973

As described, pharmacokinetic analysis with WAPPS-HEMO was performed in a subset of 14 patients from the Malmö cohort treated with BAY 81–8973. The median age was 33.5 years (IQR 18.8–43.3) and the median BMI 26.1 kg/m^2 (IQR 21.6–28.9). The median ABR and AJBR was 0 (IQR 0-0 for both). The WAPPS-Hemo estimated median t½ for BAY 81–8973 was 20 h (IQR 17–26.5) and the median estimated time to 1% was 91.5 h (IQR 59.8–143). As expected, there was a significant correlation between VWF:Ag levels and FVIII half-life (*P* .01) (Figure S1). Notably, the three patients with the shortest t1/2 (patient #6, #17 and # 18) had VWF:Ag levels 50–70 IU/dl and the three patients with the longest t1/2 (patient #1, #8 and #16) had VWF:Ag levels ≥ 170 IU/dl. If these outliers were excluded from analysis, the remaining eleven patients had a median t1/2 of 13.4 h (IQR 11.5–16.5). The data on half-life and time to 1% trough is presented on Table 1.

3.4 | Joint health status

Joint health data was available for 39 of 40 included patients (Table S1). The median HJHS score was 14 (IQR 5.5–27.0). The HJHS score revealed arthropathy, as defined by HJHS > 10, in 25 patients with median HJHS 19 (IQR 14.0–35.5). The high HJHS was predominantly due to decreased mobility in the elbow, knee, and ankle joints, decreased muscle strength, and gait problems., whereas patients with low HJHS scores received points for crepitations. Crepitus on motion may indicate cartilage damage, but no functional impairment was observed in those cases. There was no correlation (*P* .525) between bleeding events during the study period (ABR and AJBR > 0) and arthropathy (HJHS ≥10) (Table S3). None of the patients had target joints. No significant difference was observed in HJHS score between the severe HA patients of the Malmö and Oslo centres (Table 2).

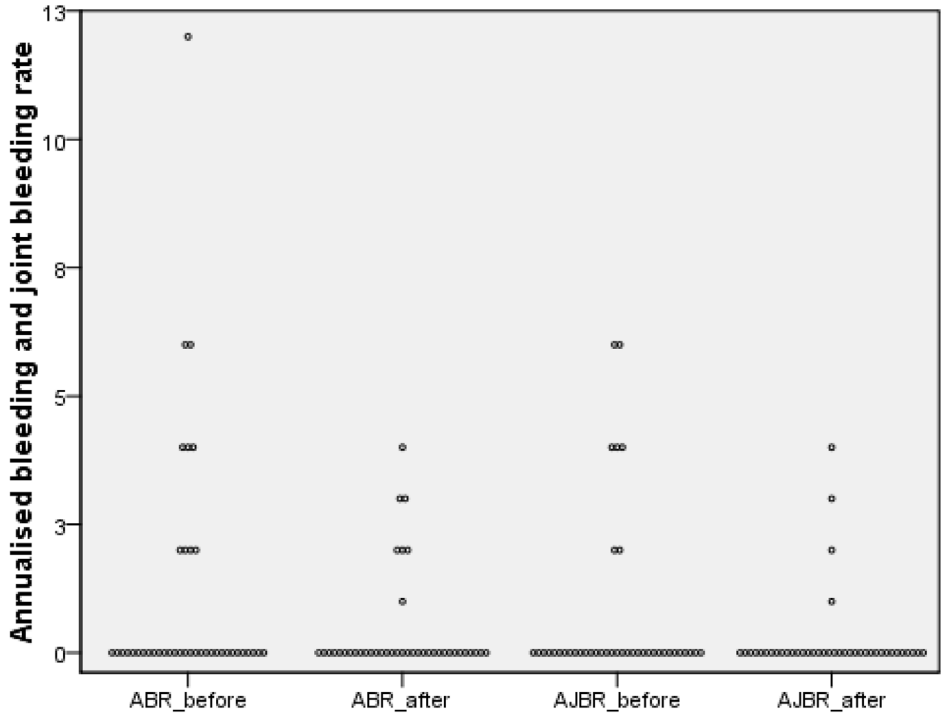
3.5 | Adherence to treatment

The complete VERITAS-Pro data is presented in Table S3. The VERITAS-Pro questionnaire was available in 34 of 40 included patients with a median score of 40 (IQR 30.8-47) (Table S1). Low scores were observed in "dosing", "planning", "skipping" and "remembering" (median 4–6, IQR 4–8). However, high scores were seen in "communication" (median 9, IQR 6–12). When a cut-off of 57 points was used to define non-adherence, only one patient scored above that threshold, signifying 97% adherence. No significant difference was observed in VERITAS-PRO score between the Malmö and Oslo centres (Table 2).

4 | DISCUSSION

The aim of this study was to examine whether the switch from a standard half-life FVIII products to BAY 81–8973, which has been reported to provide a beneficial PK compared to other SHLs[7,10] may influence clinical outcome in patients with HA. The PK analysis performed on 14 patients on BAY 81–8973 with WAPPS-HEMO confirmed a relatively favourable median half-life estimate of 20 h. for BAY 81–8973, which is longer than reported for other SHL products,[6,9,10,32] with a wide range of half-lives from 7.5 to 29 h (Table 1). Interestingly, a similar range of 9.95–22.2 h, was seen in the study by Shah et al.[9] However, inter-study differences in design, FVIII wash-out and dosing and the low subject number should be considered when interpreting these results. Additionally, due to the non-interventional design of the study,

A.



B.

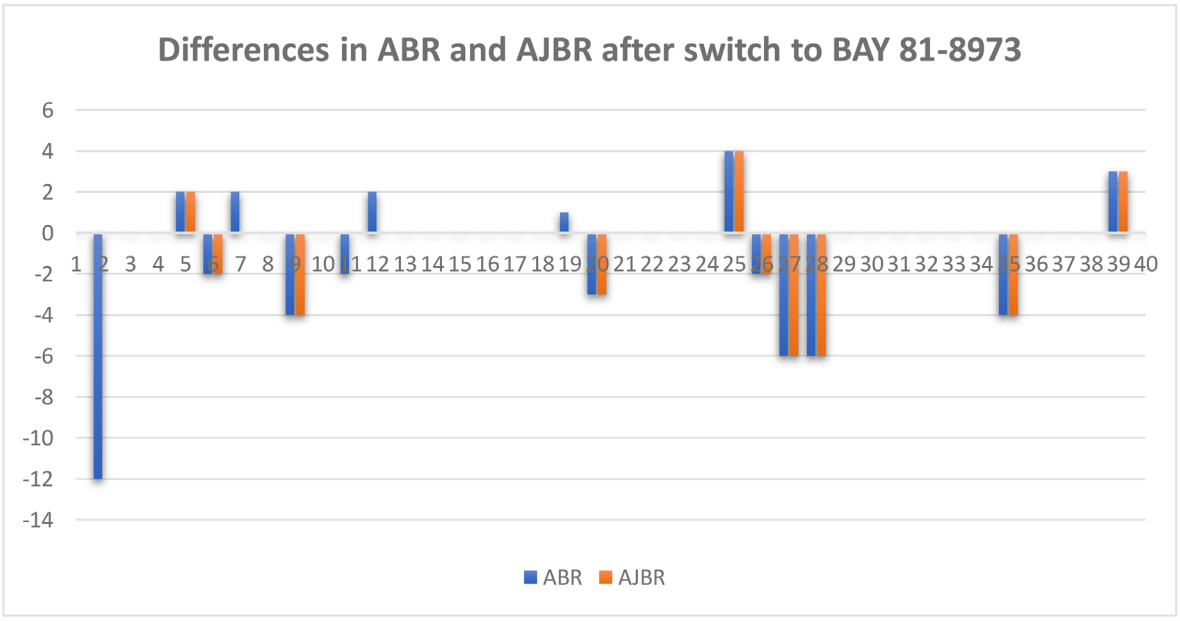


FIGURE 1 A. 2D-dot plot showing ABR and AJBR before and after switch to BAY 81-8973, respectively. Every dot symbolizes one patient B. Bar-chart showing difference in ABR and AJBR in all 40 patients of the cohort after switch to BAY 81-8973. Negative values indicate reduction in ABR and AJBR after the switch, whereas positive values indicate increase, respectively. These differences were not statistically significant.

a control group could not be evaluated. Furthermore, we observed a significant correlation to the VWF levels in our cohort,[25] and after exclusion of outliers with supranormal VWF levels, the median half-life was reduced to 13.4 h. This shows the importance to consider VWF levels when interpreting FVIII PK data and reinforces the use of head-to-head cross-over studies when comparing different products. Our data also showed that the patients overall were well treated with median ABR and AJBR of 0 both prior to and after the switch to BAY 81–8973. In absolute figures, there was a minor reduction in mean ABR and AJBR rates after the switch to BAY 81–8973, while maintaining the same

dose and dosing frequency, but this reduction was not statistically significant.

The majority of patients in our study (62.5%) had established arthropathy, but no target joints, which partly, in some cases, may be due to advanced arthropathy and fibrotic degeneration. There was no correlation between bleed rates, factor consumption and the degree of arthropathy Importantly, only 30% of our cohort were treated with high-dose prophylaxis, as defined by the World Federation of Haemophilia (WFH) cut-off of 4,000 IU/kg/year, indicating the benefits of individualized prophylaxis based on the observed individual bleeding phenotype.[23] Instead, 60% of the patients were receiving an intermediary-dose prophylaxis regimen (cut-off of 1500–4000 IU/Kg/year),[23] while still maintaining a median ABR of 0. The benefit of individualized dosing for medical outcome and factor consumption has previously been reported in a study comparing Swedish and Dutch dosing regimens[28] and these findings are further supported by our study. However, the switch to BAY 81–8973 did not lead to additional individualization of the treatment regimen.

The overall adherence to treatment in our cohort, as measured by VERITAS-Pro, was excellent, with 97% overall adherence and no difference was observed between the two centres. The adherence rate in our Scandinavian cohort was comparable to that of a German cohort (adherence 93.1%),[30] and higher than the American cohort in the original validation study (adherence 82%).[29] All the patients in our cohort had their follow-up at a specific Haemophilia centre, a strong predictor of adherence.[30] Our results also support the previously described association between good adherence and low reported bleeding events.[33]

Interestingly, we found significant differences in the yearly factor VIII consumption between the patients with severe HA treated at the two participating haemophilia centres, despite the use of the same Nordic guidelines. The Malmö centre had a lower absolute number of mean ABR and AJBR, but the difference was not significant and there was no difference in arthropathy. The difference in factor consumption was mainly due to an overall more frequent administration and shorter intervals in the Malmö cohort. However, the two groups were not matched, and recruitment bias cannot be ruled out, since all patients on prophylaxis with BAY 81–8973 were enrolled at the Malmö centre, but one half of those in Oslo. To appreciate any bias in the data collection from Oslo, the overall dosing regimen in patients on BAY 81–8973 was anonymously captured in the register. The treatment profile was similar besides more patients overall on every other day regimen instead of three times weekly. This may suggest that consumption in Oslo was overall slightly higher that observed in our enrolled subcohort. Nevertheless, our findings indicate that very low bleed rates can be achieved with relatively low FVIII consumption with entailed cost benefits. Furthermore, our findings indicate the value of PK estimations in optimizing treatment, as patients in Malmö with favourable PK profiles and low ABR could potentially extend the interval between doses.

Our study had several limitations, including the retrospective design and subjective paper-based reporting of bleeds, where potential differences in reporting and documentation practices between different centres may influence how bleeds are registered. Additionally, there was no control group and pre-infusion levels collected for the PK analysis and no validation step was performed to confirm the PK estimates. Due to the very low reported ABR and AJBR, our study was probably underpowered in detecting statistical correlations between bleeding rates and arthropathy or adherence to treatment. However, this may reflect the importance of an effective treatment plan and close follow-up of patients in ameliorating the impact of these variables on the bleeding phenotype. Finally, as previously stated, selection bias cannot be ruled out due to the relatively low enrolment at the Oslo centre.

In conclusion, in a cohort of previously well treated and well-adherent patients, the switch to BAY 81–8973, with a potential favourable half-life, achieved marginal improvements on already favourable outcome rates despite the use of mainly intermediate-intensity regimens. Our study also showed that a high degree of established arthropathy and lower annual FVIII consumption do not necessarily result in increased bleed rates. Instead, individualized prophylaxis regimens and close follow-up with high adherence to treatment, can reduce FVIII consumption while maintaining haemostatic efficacy. The data further underline that, not only the performance of the single product brand, but how to use the products is important for the outcome in the individual patient.

ACKNOWLEDGEMENTS

This study was funded through an unrestricted research grant from Bayer. The authors would like to thank Karin Strandberg at Labmedicin Skåne for fruitful collaboration.

AUTHOR CONTRIBUTIONS

AA and JA designed the study, acquired, analysed, and interpreted the data, drafted and finalized the manuscript. PAH recruited patients, interpreted the data and finalized the manuscript. EB designed the study, interpreted the data and finalized the manuscript.

CONFLICT OF INTEREST

AA has received research grants from Takeda/Shire and Bayer. Speaker's fee and consultant for Ablynx/Sanofi, Sobi, Chiesi, Amgen. PAH has received research grants to institution from Bayer, Octapharma, Pfizer and SOBI. Speaker's fee and consultant for Bayer, Takeda, Octapharma, Pfizer, NovoNordisk and SOBI. EB has acted as paid consultant to Bayer, CSL Behring, Octapharma, Sobi, Takeda, and has received funding for research from Sobi and Bioverativ. EB has acted as paid consultant to Bayer, CSL Behring, Octapharma, Sobi, Takeda, and has received funding for research from Sobi and Bioverativ. JA has received research grants from Sobi, CSL Behring, Takeda/Shire, and Bayer. Speaker's fee and consultant for Octapharma, Novo Nordisk, Pfizer, Bayer, Sobi, Sanofi, CSL Behring, Takeda/Shire, BioMarin and Uniqure.

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.

ORCID

Alexandros Arvanitakis https://orcid.org/0000-0001-9371-9396

Erik Berntorp https://orcid.org/0000-0002-2888-4931

Jan Astermark https://orcid.org/0000-0001-8500-2483

REFERENCES

1. Berntorp E, Shapiro AD. Modern haemophilia care. *Lancet*. 2012; 379(9824): 1447-1456.
2. Astermark J, Petrini P, Tengborn L, Schulman S, Ljung R, Berntorp E. Primary prophylaxis in severe haemophilia should be started at an early age but can be individualized. *Br J Haematol*. 1999; 105(4): 1109-1113.
3. Nilsson IM, Berntorp E, Löfqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med*. 1992; 232(1): 25-32.
4. Shapiro AD. Anti-hemophilic factor (recombinant), plasma/albumin-free method (octocog-alpha; ADVATE) in the management of hemophilia A. *Vasc Health Risk Manage*. 2007; 3(5): 555-565.
5. Lusher JM, Scharrer I. Evolution of recombinant factor VIII safety: KOGENATE and Kogenate FS/Bayer. *Int J Hematol*. 2009; 90(4): 446-454.
6. Di Paola J, Smith MP, Klamroth R, et al. ReFacto and Advate: a single-dose, randomized, two-period crossover pharmacokinetics study in subjects with haemophilia A. *Haemophilia*. 2007; 13(2): 124-130.
7. Keating GM. BAY 81–8973 (Octocog Alfa; Kovaltry(®)): a Review in Haemophilia A. *BioDrugs*. 2016; 30(5): 453-459.
8. Mahlangu J, Young G, Hermans C, Blanchette V, Berntorp E, Santagostino E. Defining extended half-life rFVIII-A critical review of the evidence. *Haemophilia*. 2018; 24(3): 348-358.
9. Shah A, Delesen H, Garger S, Lalezari S. Pharmacokinetic properties of BAY 81–8973, a full-length recombinant factor VIII. *Haemophilia*. 2015; 21(6): 766-771.
10. Shah A, Solms A, Garmann D, et al. Improved pharmacokinetics with BAY 81–8973 versus antihemophilic factor (recombinant) plasma/albumin-free method: a randomized pharmacokinetic study in patients with severe hemophilia A. *Clin Pharmacokinet*. 2017; 56(9): 1045-1055.
11. Collins PW, Björkman S, Fischer K, et al. Factor VIII requirement to maintain a target plasma level in the prophylactic treatment of severe hemophilia A: influences of variance in pharmacokinetics and treatment regimens. *J Thromb Haemost*. 2010; 8(2): 269-275.
12. Iorio A, Keepanasseril A, Foster G, et al. Development of a web-accessible population pharmacokinetic service-hemophilia (WAPPS-Hemo): study protocol. *JMIR Res Protoc*. 2016; 5(4): e239.
13. Iorio A. Using pharmacokinetics to individualize hemophilia therapy. *Hematology Am Soc Hematol Educ Program*. 2017; 2017(1): 595-604.
14. Björkman S, Collins P. Measurement of factor VIII pharmacokinetics in routine clinical practice. *J Thromb Haemost*. 2013; 11(1): 180-182.
15. Carlsson M, Berntorp E, Björkman S, Lindvall K. Pharmacokinetic dosing in prophylactic treatment of hemophilia A. *Eur J Haematol*. 1993; 51(4): 247-252.
16. Carlsson M, Berntorp E, Björkman S, Lethagen S, Ljung R. Improved cost-effectiveness by pharmacokinetic dosing of factor VIII in prophylactic treatment of haemophilia A. *Haemophilia*. 1997; 3(2): 96-101.
17. Knobe K, Berntorp E. Haemophilia and joint disease: pathophysiology, evaluation, and management. *J Comorb*. 2011; 1: 51-59.
18. Khawaji M, Astermark J, Von Mackensen S, Akesson K, Berntorp E. Bone density and health-related quality of life in adult patients with severe haemophilia. *Haemophilia*. 2011; 17(2): 304-311.
19. Rodríguez-Merchán EC. Pathogenesis, early diagnosis, and prophylaxis for chronic hemophilic synovitis. *Clin Orthop Relat Res*. 1997(343): 6-11.
20. van Vulpen LFD, Holstein K, Martinoli C. Joint disease in haemophilia: pathophysiology, pain and imaging. *Haemophilia*. 2018; 24 Suppl 6: 44-49.
21. Krishnan S, Vietri J, Furlan R, Duncan N. Adherence to prophylaxis is associated with better outcomes in moderate and severe haemophilia: results of a patient survey. *Haemophilia*. 2015; 21(1): 64-70.
22. Carlsson KS, Höjgård S, Lindgren A, et al. Costs of on-demand and prophylactic treatment for severe haemophilia in Norway and Sweden. *Haemophilia*. 2004; 10(5): 515-526.
23. Srivastava A, Santagostino E, Dougall A, et al. WFH guidelines for the management of hemophilia. *Haemophilia*. 2020; 26 Suppl 6: 1-158.
24. Antovic J, Nordic Hemophilia Guidelines. 2020.
25. Kepa S, Horvath B, Reitter-Pfoertner S, et al. Parameters influencing FVIII pharmacokinetics in patients with severe and moderate haemophilia A. *Haemophilia*. 2015; 21(3): 343-350.
26. Feldman BM, Funk SM, Bergstrom BM, et al. Validation of a new pediatric joint scoring system from the International Hemophilia Prophylaxis Study Group: validity of the hemophilia joint health score. *Arthritis Care Res (Hoboken)*. 2011; 63(2): 223-230.
27. van Galen KPM, de Kleijn P, Foppen W, et al. Long-term impact of joint bleeds in von Willebrand disease: a nested case-control study. *Haematologica*. 2017; 102(9): 1486-1493.
28. Fischer K, Steen Carlsson K, Petrini P, et al. Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s. *Blood*. 2013; 122(7): 1129-1136.
29. Duncan N, Kronenberger W, Roberson C, Shapiro A. VERITAS-Pro: a new measure of adherence to prophylactic regimens in haemophilia. *Haemophilia*. 2010; 16(2): 247-255.
30. Miesbach W, Kalnins W. Adherence to prophylactic treatment in patients with haemophilia in Germany. *Haemophilia*. 2016; 22(5): e367-374.
31. Iorio A, Blanchette V, Blatny J, Collins P, Fischer K, Neufeld E. Estimating and interpreting the pharmacokinetic profiles of individual patients with hemophilia A or B using a population pharmacokinetic approach: communication from the SSC of the ISTH. *J Thromb Haemost*. 2017; 15(12): 2461-2465.
32. Klamroth R, Simpson M, von Depka-Prondzinski M, et al. Comparative pharmacokinetics of rVIII-SingleChain and octocog alfa (Advate(®)) in patients with severe haemophilia A. *Haemophilia*. 2016; 22(5): 730-738.
33. Dover S, Blanchette VS, Wrathall D, et al. Hemophilia prophylaxis adherence and bleeding using a tailored, frequency-escalated approach: the Canadian hemophilia primary prophylaxis study. *Res Pract Thromb Haemost*. 2020; 4(2): 318-325.

SUPPORTING INFORMATION

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

How to cite this article: Arvanitakis A, Holme PA, Berntorp E, Astermark J. Clinical outcome and adherence rate in Scandinavian patients with intermediate-intensity prophylaxis before and after the switch of standard half-life FVIII products to BAY 81–8973. *Haemophilia*. 2022;1-7. https://doi.org/10.1111/hae.14489