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Long-term clinical and economic outcomes in previously untreated paediatric patients with severe haemophilia A: A nationwide real-world study with 700 person-years

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Aim: For previously untreated patients (PUPs) with severe haemophilia A in Finland for the past 2 decades, the standard practice has been to start early primary prophylaxis. We evaluated the long-term clinical outcomes and costs of treatment with high-dose prophylaxis in PUPs from birth to adolescence, including immune tolerance induction (ITI).

Methods: From the medical records of all PUPs born between June 1994 and May 2013 in Finland, we retrospectively extracted data on clinical outcomes and health-care use. Using linear mixed models, we analysed longitudinal clinical outcome data. To analyse skewed cost data, including zero costs, we applied hurdle regression.

Results: All 62 patients received early regular prophylaxis; totally, they have had treatment for nearly 700 patient-years. The median age of starting home treatment was 1.1 years. The mean (SD) annual treatment costs (€ per kg) were 4391€ (3852). For ages 1-3, ITI comprised over half of the costs; in other groups, prophylactic FVIII treatment dominated. With these high costs, however, clinical outcomes were desirable; median (IQR) ABR was low at 0.19 (0.07-0.46) and so was AJBR at 0.06 (0-0.24). Thirteen (21%) patients developed a clinically significant inhibitor, 10 (16%) with a high titre. All ITIs were successful. The mean costs for ITI were 383 448€ (259 085). The expected ITI payback period was 1.81 (95% CI 0.62-12.12) years.

Conclusions: Early high-dose prophylaxis leads to excellent long-term clinical outcomes, and early childhood ITI therapy seems to turn cost-neutral generally already in 2 years.

KEYWORDS
ABJR, ABR, bleed, costs, haemophilia A, health economics, outcome, prophylaxis, PUP

1 | INTRODUCTION

Severe haemophilia A (FVIII: C < 0.01 IU/mL) is a congenital X-linked bleeding disorder resulting in spontaneous and trauma-induced bleeds, especially in joints. Prophylactic replacement therapy with clotting factor VIII (FVIII) concentrates has augmented the prevention of the development of haemophilic arthropathy 459[1]; 460[2]. It offers patients a near-normal life with a life expectancy similar to that of males in the general population 461.[3] Prophylactic FVIII treatment also associates with a decreased inhibitor development risk 413.[4] Hence, early regular prophylaxis is the standard of care in children with severe haemophilia. Haemophilia treatment costs are high, with high-dose prophylaxis accounting for 95%-99.6% of the total 500[5]; 455.[6] The predicted annual total treatment costs for an average-weight (74 kg) adult noninhibitor patient exceed US$ 298 000. Paediatric cost studies with real-world data are few; an estimate of the average total annual costs of treating patients is US$ 21 600 for young children and US$ 124 000 for teenagers 469[7]; 464[8]; 472.[9] Most treatment cost reports are per patient and usually not per body weight, which challenges the cost comparisons. This is typical among different paediatric studies where patient body weight varies significantly, and yet dosing is based on weight.

In Finland, the treatment of all children with severe haemophilia either in comprehensive care or haemophilia treatment centres in university hospitals follows a uniformly agreed protocol. Here, it has been a standard practice for nearly 2 decades to start primary prophylaxis with a recombinant FVIII (rFVIII) for all patients below age one, mainly via a central venous access device (CVAD) without increasing the risk of inhibitor development 465[10]; 452.[11] With a long follow-up, this nationwide study evaluated the long-term real-world outcomes and yearly patient weight-based total costs in previously untreated patients (PUPs) with severe haemophilia A with and without inhibitors. We also included the costs of immune tolerance induction (ITI). We hope the study will pave the way to uniform documentation of treatment costs of paediatric haemophilia.

2 | MATERIALS AND METHODS

2.1 | Design and setting

This 19-year retrospective, nationwide, real-world, multicentre study evaluated the clinical outcomes and direct medical costs of the treatment of PUPs with severe haemophilia A (FVIII coagulation activity <0.01 IU/mL) in Finland. We enrolled all PUPs (n = 62) born between June 1994 and May 2013 who had at least 75 exposure days (EDs) of concentrate use or who developed inhibitors until the end of the follow-up in September 2013. The patient cohort was the same as in our previous PUP study on inhibitor development in Finland 452.[11] The study involved 5 Finnish paediatric Haematology-Oncology tertiary centres (Kuopio, Oulu, Turku, Tampere and Helsinki University Hospitals), which serve also as treatment centres of haemophilia for children and adolescents.

The Research Ethics committee of Northern Savo, Finland, provided a favourable opinion for this study (26//2010). We obtained permissions to use the register data from each organization concerned.

2.2 | Data extraction

The principal investigator (KV) collected detailed medical history data from all these patients' medical records. Patient and treatment characteristics data included date of birth and diagnosis, ethnicity, first exposure to FVIII (age and indication), prophylaxis with coagulation factor concentrates, and treatment of bleeding episodes and surgical procedures with an FVIII concentrate or with bypassing agents (recombinant activated factor VII [rFVIIa] and plasma-derived activated prothrombin complex concentrate [aPCC]), inhibitor development and ITI therapy. Patient-specific data included clinical outcomes including ITI success, coagulation factor concentrate consumption and the utilization of healthcare services; for this last item, we used the top-down costing approach, where extracted individual services were valued by the national tariffs 466.[12]

2.3 | Prophylaxis

Detailed individual data on prophylaxis included age, type of venous access, number of exposure days and previous joint bleeds at the onset of prophylaxis. It also included the annual prophylactic regimen for every patient including body weight, dosage and frequency of prophylactic FVIII administrations. "Regular prophylaxis" was defined as long-term uninterrupted administration of an FVIII concentrate at least once a week to prevent bleeds. "Primary prophylaxis" meant regular prophylaxis started before age 2 and before the onset of any joint bleed. "Secondary prophylaxis" covers all other long-term prophylactic regular treatments failing to fulfil the criteria of primary prophylaxis.

2.4 | Clinical outcomes and bleeding episodes

We observed the number of annual bleeds including joint bleeds and the number of patients with a target joint or an arthropathy. We calculated the annualized bleeding rate (ABR) and the annualized joint bleeding rate (AJBR) as the number of (joint) bleeding episodes divided by the length of follow-up time in years. We recorded all major and minor bleeds requiring hospitalization. We based our definition of a major bleed in surgical and nonsurgical settings on ISTH recommendations 453[13]; 418.[14] A joint bleed meant an episode characterized by an unusual sensation or "aura" in the joint in combination with any of the following signs: (i) increasing swelling or warmth of the skin over the joint, (ii) increasing pain, and (iii) progressive loss of range or difficulty in using the limb as compared to the baseline 447[15]; 448.[16] In infants and young children, a joint bleed meant reluctance to use the limb accompanied with either pain, or swelling or warmth of the skin over the joint.

A target joint was defined as 3 or more spontaneous bleeds in a single joint within 6 consecutive months 447[15]; 448.[16] A chronic haemophilic arthropathy meant a target joint with clinical or radiological evidence of significant synovitis 448.[16]

2.5 | Inhibitor development and immune tolerance induction

Clinically significant inhibitor development was defined as at least 2 positive antibody titres combined with a decreased in vivo FVIII recovery 251.[17] High-titre inhibitors occurred when the peak inhibitor titre was at least 5 Bethesda Units (BU)/mL. We classified as "low responders" (LRs) patients with inhibitor titres persistently ≤5 BU/mL despite repeated challenges with FVIII; "high responders" (HRs) referred to patients with inhibitor titres >5 BU/mL at any time 447.[15] Low responders received 50-150 IU FVIII kg^{-1} daily, or thrice a week; high responders received 100 IU FVIII kg^{-1} every 12 hours, or 100-200 IU FVIII kg^{-1} daily. We based our definition of ITI success in terms of successful tolerance and partial response on the criteria of the International ITI (I-ITI) study and U.S. guidelines for immune tolerance induction (Table 1) 450[18]; 451.[19]

2.6 | Healthcare resource use and costs

To estimate the long-term costs of treatment, we recorded the use of all clotting factor concentrates and healthcare services. The former included FVIII, rFVIIa and pd-aPCC use for prophylaxis, bleeds and for surgical procedures, and FVIII use for ITI. The latter comprised the number of hospitalizations for bleeding episodes or surgical procedures and the length of stay for each hospitalization, including the number of days in the ICU. We also recorded the numbers of outpatient visits, CVAD insertions and removals, and CVAD-related infections. The unit costs of the services utilized (Table 2) were obtained from the national healthcare unit cost list 473,[20] and all costs were assessed at real values (€) in 2014. The estimated costs are convertible to US$ using the European Central Bank annual bilateral exchange rates in 2014 available at sdw.ecb.europa.eu. We report all costs by weight adjustment, that is per kg of body weight to describe and compare costs between patients of different ages and weights.

2.7 | Validation

To validate the FVIII consumption data extracted from the medical records, we acquired a patient-specific validation sample from the Finnish Prescription Register maintained by the Social Insurance Institution (SII). This database of nationwide electronic pharmacy reimbursement claims became available in 1994, and it includes records of all medication dispensations reimbursed to community-dwelling residents of Finland. The register keeps no record of nonreimbursed medications or medications dispensed during a hospital stay 468.[21] Our validation data sample included all study patients, except children living in the area of the hospital district of Helsinki and Uusimaa. Prior to SII data collection, all patients,

TABLE 1 Patient and treatment characteristics

PUPs with severe haemophilia A	62
Caucasian (%)	60 (97)
Median age at diagnosis, months (range)	0.7 (0-14.8)
Median age at first exposure to FVIII, months (range)	9.0 (0-16.2)
Median age at the end of follow-up, years (range)	12.7 (1.2-19.3)
Cumulative follow-up time, years	698
Prophylactic regimen	
Patients with regular prophylaxis[a] (%)	62 (100)
Median age at the onset of regular prophylaxis, months (range)	11.8 (0.8-51.2)
Type of a venous access at the onset of prophylaxis	
Peripheral veins (%)	5 (8)
CVAD (%)	57 (92)
Median age at start of home treatment, years (range)	1.1 (0.2-4.3)
Patients with primary prophylaxis[b] (%)	51 (82)
Patients with secondary prophylaxis[c] (%)	11 (18)
Type of initial FVIII concentrate used	
pd-FVIII products	23 (37)
rFVIII products	39 (63)
Median dose of prophylactic FVIII, IU/kg (IQR)	26 (22-32)
Median frequency of prophylactic infusions per week (IQR)	3 (3-3.5)
Median yearly dose of FVIII, IU/kg (IQR)	4136 (3250-5113)
Inhibitor development	
Patients who developed inhibitors (%)	13 (21)
High-titre[d] inhibitors (%)	10 (16)
Median peak titre, BU/mL (range)	14 (1.7-42)
Median age at ID, months (range)	11.7 (7.2-27.7)
Median ED at ID (range)	19 (10-61)
ITI success	
Patients who started ITI	12
Patients who completed ITI	11
Patients with successful tolerance[e] (%)	4 (36)
Patients with partial response[f] (%)	7 (64)

PUPs, previously untreated patients; FVIII, coagulation factor VIII; CVAD, central venous access device; IQR, interquartile range; BU, Bethesda unit; ID, inhibitor development; ED, exposure days; ITI, immune tolerance induction.

[a]Regular prophylaxis, regular and long-term administration of FVIII concentrate at least once a week to prevent bleeds.

[b]Primary prophylaxis, regular prophylaxis started before the age of 2 y and before the onset of the first joint bleed.

[c]Secondary prophylaxis, regular prophylaxis started later than the age of 2 y or after the first joint bleed.

[d]High-titre inhibitor was defined as a peak inhibitor titre ≥5 BU/mL.

[e]Successful tolerance, a persistently negative inhibitor titre (<0.6 BU/mL), FVIII recovery ≥66% of expected and FVIII half-life ≥6 h.

[f]Partial response, after 33 mo of ITI, a negative inhibitor titre, but persistently abnormal FVIII recovery or half-life; the patient responds clinically to FVIII replacement without an anamnestic increase in inhibitor titre.

their parents, or both, provided written informed consent. The validation was conducted by comparing median annual prophylactic FVIII consumption estimate obtained from the medical records with the total amount of FVIII dispensed obtained from the SII registry.

2.8 | Statistical analysis

Descriptive statistics as mean and standard deviation (SD) or median and inter-quartile range (IQR) are presented; categorical variables are reported as frequencies and proportions. We analysed longitudinal outcome data using a linear mixed model for repeated measures. Hurdle modelling approach was applied to right-skewed cost data including excess zero values. Furthermore, nonparametric bootstrapping was applied to define 95% confidence intervals for mean cost estimates.

To demonstrate the potential economic value of ITI, an expected payback period estimate in years was provided to indicate the time period of cost savings (after the completing of ITI) needed to equal the overall cost of ITI. To estimate the expected length of the payback period, the average costs of ITI were compared with the costs of an expected alternative treatment strategy without ITI, that is a treatment with prophylactics or on-demand therapy with bypassing agents. The payback analysis included all patients who completed ITI, except one with ID recurrence, to describe the average costs for ITI carried out during early childhood. Nonparametric bootstrapping with replacements was applied to define 95% confidence intervals for the payback period estimate. Linear mixed model for repeated-measures was performed by SPSS software version 21 (IBM Corp., Armonk, NY, USA). Hurdle regression analysis with bootstrapping was executed by R statistical software version 3.1.1 using function hurdle in R package pscl. P-values <.05 indicated statistical significance.

3 | RESULTS

3.1 | Patient characteristics

The final study sample included 62 PUPs with severe haemophilia A. We excluded 7 patients: 4 immigrants were PTPs, previously treated with an unknown amount of an unidentified factor concentrate and blood components for bleeds, and 3 children had less than 75 exposure days. One child with a severe immunodeficiency, a chronic granulomatous disease, was included in the study, without recording the costs unrelated to haemophilia care, such as costs related to the treatment at the stem cell transplantation unit. The patients were not diagnosed with any other severe conditions or bleeding disorders.

The median follow-up time for these patients was 12.7 years (range 1.2-19.3), with a cumulative follow-up time of 698 person-years. During the follow-up, 13 (21%) children developed a clinically significant inhibitor, 10 (16%) a high-titre one. Table 1 shows the baseline characteristics of the study population.

TABLE 2 Unit costs

Recourse use	Price in €*	Source
FVIII product (per IU)	0.69	Market share weighted price per IU (excluding VAT)
rFVIIa (per μg)	0.64	Market share weighted price per IU (excluding VAT)
pd-aPCC (per IU)	0.85	Market share weighted price per IU (excluding VAT)
Hospital day/ Ward day	931	(12)
ICU day	3803	(12)
nICU day	2716	(12)
Visit to outpatient clinic	294	(12)
CVAD insertion	963	Kuopio University Hospital tariff
CVAD removal	813	Kuopio University Hospital tariff

rFVIIa, recombinant activated factor VII; pd-aPCC, plasma-derived activated prothrombin complex concentrate; ICU, intensive care unit; nICU, neonatal intensive care unit; CVAD, central venous access device.
* Prices at real values in 2014.

3.2 | Treatment

All our patients were on regular prophylaxis. Fifty-one (82%) fulfilled the criterion of primary prophylaxis, while 11 children (18%) had secondary prophylaxis initiated. The median age of starting home treatment was 1.1 years. During the follow-up, the median frequency of prophylactic FVIII concentrate infusions was 3 times a week, with a median dose of 26 IU/kg (IQR, 22-32). The median annual FVIII used in prophylaxis was 4136 IU/kg (IQR, 3250-5113). Trough levels of FVIII were used to guide prophylactic treatment in 11 patients (18%). Table 1 presents treatment characteristics.

3.3 | Validation

When comparing the annual prophylactic FVIII consumption extracted from the medical records with the patient-specific data obtained from the Finnish Prescription Register (2012), we did not find significant differences among the patients included in the validation sample. The prophylactic FVIII median consumption observed was 4136 IU/kg (IQR, 3250-5113) in the medical record data and 4722 IU/kg (IQR, 3510-5777) in the national register data.

3.4 | Long-term clinical outcomes

Tables 3 shows long-term clinical outcomes. During the follow-up, 25 (40%) of the patients experienced no joint bleeds, while 19 (31%) had one or two. Median ABR was 0.19 (IQR, 0.07-0.46), and AJBR was 0.06 (IQR, 0-0.24). Inhibitor development was a significant risk factor for a higher overall bleed rate, but not for a higher joint bleed

	All patients, n = 62	Non-inhibitor patients, n = 49	Patients with an inhibitor history, n = 13	P
ABR, median (IQR)	0.19 (0.07-0.46)	0.16 (0.03-0.33)	0.49 (0.22-0.83)	<.001
AJBR, median (IQR)	0.06 (0-0.24)	0.06 (0-0.21)	0.15 (0-0.26)	.26
Patients with 0 joint bleed, n (%)	25 (40)	21 (43)	4 (31)	.32
Patients with 1 joint bleed, n (%)	15 (24)	12 (25)	3 (23)	
Patients with 2 joint bleeds, n (%)	4 (7)	3 (6)	1 (8)	
Patients with ≥3 joint bleeds, n (%)	18 (29)	13 (26)	5 (38)	
Patients with a target joint, n (%)	10 (16)	9 (18)	1 (8)	.68
Patients with arthropathy, n (%)	4 (6)	4 (8)	0 (0)	.26
Hospital in-patient days, per year, median (IQR)	2.5 (1.4-4.2)	2.4 (1.3-4)	3.9 (1.9-7.5)	.09
Visits in outpatient clinic, per year, median (IQR)	2.2 (2.0-3.0)	2.0 (1.9-3)	2.7 (2.4-3.9)	<.01

PUPs, previously untreated patients; ABR, annual bleeding rate; AJBR, annual joint bleeding rate; IQR, interquartile range.

rate; ABR was 0.16 in noninhibitor patients; whereas in inhibitor patients it was 0.49 ($P < .001$). AJBR was 0.06 in noninhibitor patients, and in inhibitor patients it was 0.15 ($P = .26$).

In contrast, ABR and AJBR were 3- to 4-fold lower among primary prophylaxis patients (0.17 and 0. 06) compared with patients who received secondary prophylaxis (0.52 and 0.26) ($P = .04$, and $P = .001$, respectively). Four noninhibitor patients (6%) had a traumatic intracranial bleed early in their childhood. No deaths occurred during the follow-up. Hospital in-patient days were rarely necessary (2.5 per patient annually), with approximately 2 routine annual outpatient visits to haemophilia centres.

Ten (16%) patients developed a target joint; 4 (6%) children developed chronic arthropathy, 2 of them requiring synovectomy. The incidence of a target joint or an arthropathy at the end of follow-up was 18% and 8% in noninhibitor patients and 8% and 0% in inhibitor patients (NS). Between children with primary or secondary prophylaxis, the incidence of a target joint or an arthropathy did not differ.

During these 698 patient-years of follow-up, our 62 subjects suffered 23 CVAD-related infections. They had 18 CVAD-associated bloodstream infections and 5 local tunnel infections. That means they had 3.3 CVAD-related infections per 100 person-years.

Of the 13 inhibitor patients, 12 (92%) initiated ITI; in one case with a titre drop of 45% to 15 BU/mL 4 months from ID, ITI was postponed. Eleven patients (92%) completed ITI after a median duration of 8.7 months (range 4.1-30.1), all achieving tolerance with complete or partial success. One HR remained in ITI after an 18-month therapy, with the inhibitor declining to 1.9 BU/mL). A recurrence with a

peak inhibitor titre 24 BU/mL occurred in one patient a decade after ITI, at the age of 14; 17 months of re-ITI led to complete success.

3.5 | Long-term economic outcomes

During the 698 patients-years of follow-up, the mean (SD) annual treatment costs were 97 005€ (65 465), per patient and 4391€ (3852) per weight kg. These mean annual weight-adjusted costs were 2.8-fold (95% CI 1.9-4.1) higher in the case of inhibitor patients. For patients without an inhibitor, they were 3154€ (95% CI, 2887-3446); whereas for patients with an inhibitor, they were 8691€ (95% CI, 6142-12 298, $P < .01$).

Figure 1 shows the mean costs per patient, and Figure 2 shows per patient and body weight adjustment, according to the treatment entity and age group. Prophylactic FVIII treatment accounted for the main cost, except in ages 1-3, where ITI accounted for more than half of the total costs. The mean annual costs for FVIII prophylaxis increased with age until 7, reaching 3172€ per kg (95% CI 2915-3455). Thereafter, they gradually decreased to 2246€ per kg (95% CI 1717-2857) at the age of 18. Mean annual total costs between prophylactic regimens were about the same: 4437€ per kg (95% CI 3431-5738) for patients with primary prophylaxis and 4183€ per kg (95% CI 3170-5519, $P = .76$) for those with secondary prophylaxis. The proportion of costs related to hospitalizations and outpatient visits were 51% for age 0 and 11% for age 1. However, since age 2, clotting factor consumption dominated costs, accounting for over 94% of the total costs. The group using the trough level guidance (n = 11) exhibited a
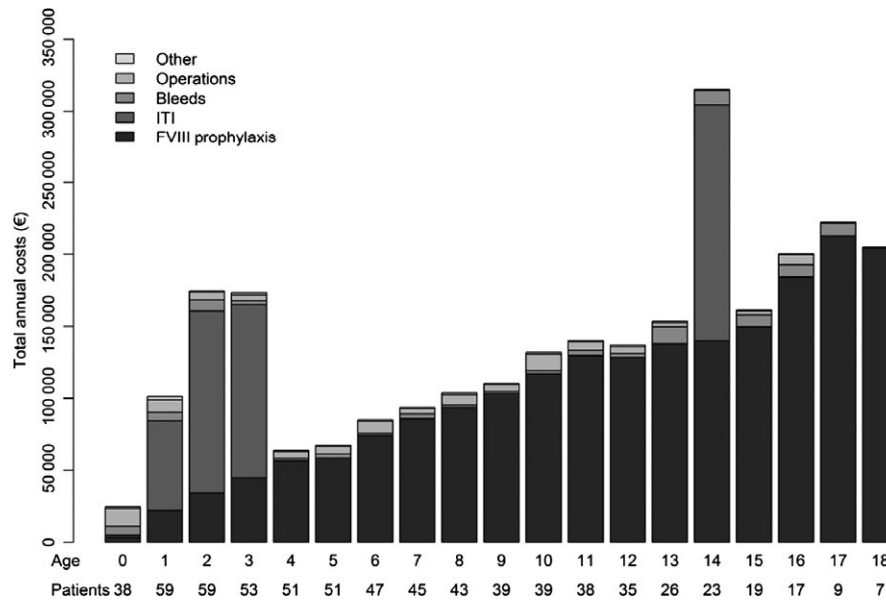
FIGURE 1 Mean total costs by age group according to a treatment entity. Bleeds: *Including costs for visits in outpatient clinic, hospitalizations and coagulation factors during the bleeding episode. Operations: ~Including costs for surgery, hospitalizations and coagulation factors. Other: #Including costs for regular hospital visits in outpatient clinic, hospitalizations for central venous access device (CVAD)-related infections and prophylaxis with rFVIIa in 2 patients
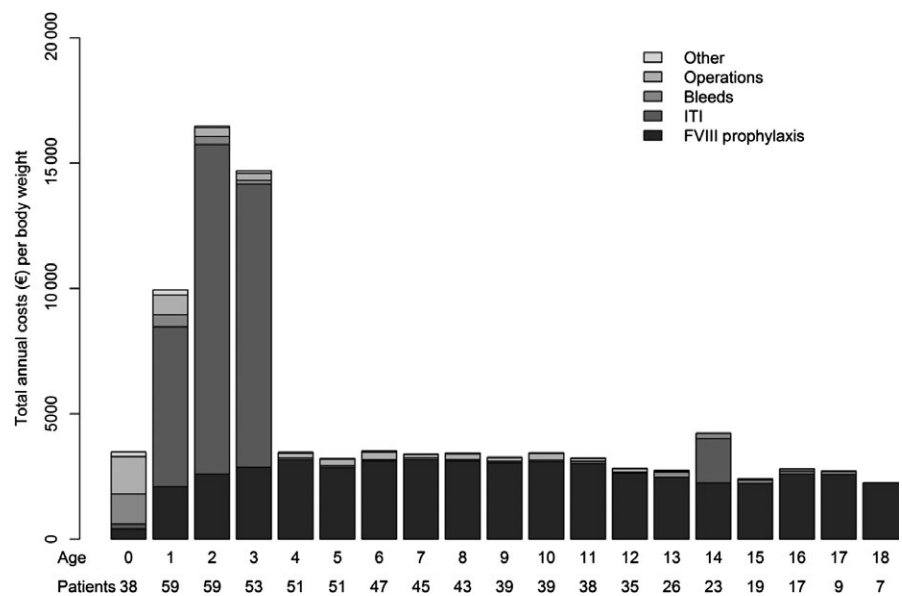

FIGURE 2 Mean total costs per weight by age group according to a treatment entity. Bleeds: *Including costs for visits in outpatient clinic, hospitalizations and coagulation factors during the bleeding episode. Operations: ~Including costs for surgery, hospitalizations and coagulation factors. Other: #Including costs for regular hospital visits in outpatient clinic, hospitalizations for central venous access device (CVAD)-related infections and prophylaxis with rFVIIa in 2 patients

trend towards lower annual prophylactic FVIII consumption (median 3645, IQR 2889-4588) compared to the group with untested trough levels (n = 51) (median 4330, IQR 3391-5200, (P = .12).

The mean (SD) cost of ITI was 383 448€ (259 085). In the patient who had an inhibitor recurrence at age 14, the costs of ITI exceeded 3 483 120€. For this boy, the first ITI cost at age 3 was 352 590€. We calculated the mean total costs per person-month and per weight for inhibitor patients based on the time period: before or after inhibitor development, and before or after ITI. After inhibitor detection, mean (SD) monthly costs in €/kg quintupled from 259 (229) up to 1473 (1984); during ITI, they further doubled to 3097 (2039).

After ITI completion, the mean monthly €/kg costs decreased to 316 (97), nearly as low as in noninhibitor patients (mean, 275, SD, 76). The expected payback period on ITI completion was 1.81 (95% CI 0.62-12.12) years, which indicates a relative short payback period in terms of annual cost savings.

4 | DISCUSSION

Our study demonstrated that regular high-dose prophylactic treatment of PUPs with severe haemophilia A leads to excellent long-term

clinical outcomes: both ABR and AJBR were very low. In patients with inhibitor development, early childhood ITI therapy was successful in terms of joint bleed rates; no difference existed between noninhibitor patients and patients with inhibitors. Early childhood ITI, regardless of its high initial costs, seems as a cost-neutral option in the long run, in fact already in <2 years, *that is* when comparing a hypothetical treatment strategy with the use of prophylactic or on-demand therapy with bypassing agents.

To the best of our knowledge, this study is the first of its kind using real-world data to examine the long-term clinical and economic outcomes of regular prophylactic treatment of PUPs with severe haemophilia A. We included inhibitor patients and provide data on costs per body weight, representing nearly 700 patient-years of follow-up. All our patients were on early regular prophylaxis started at the median age of 11.8 months. The median (IQR) annual FVIII consumption in prophylaxis was 4136 IU/kg (3250-5113). During the long follow-up (median 12.7 years), 40% of our patients experienced no joint bleed; over two-thirds (71%) experienced fewer than 3 joint bleeds. At the end of the follow-up, only 4 children had a target joint, which developed into chronic arthropathy. Thirteen (21%) patients developed a clinically significant inhibitor.

The mean (SD) overall total annual treatment costs per patient were 4391€/kg (3852). All patients who completed ITI achieved tolerance with complete (36%) or partial (64%) success. The mean (SD) total costs for ITI were 383 448€ (259 085), and at ages 1-3, ITI accounted for more than half of the total costs; whereas at age above 3, prophylactic FVIII treatment dominated.

A few long-term outcome studies of adult noninhibitor patients with regular prophylaxis have reported both clotting factor costs for prophylaxis and other healthcare costs such as surgery, hospitalizations and healthcare visits 500[5]; 455.[6] Most paediatric studies report only the costs of prophylaxis 460[2]; 459,[1] and resource utilization and related costs are only estimated with hypothetical patients 456,[22] without real-world data, which were the source of our approach. Although our study is retrospective, its advantages include long follow-up time, the uniform guidelines in Finnish paediatric haemophilia care, and the inclusion of national data of all consecutive PUPs during the 19-year study period, and all treatment costs covering the neonatal period to adolescence. Finland has centralized patient care to university hospitals, and our national haemophilia expert team of paediatric haematologists has unanimously agreed upon recommendations for treatment, prophylaxis and ITI. In addition, our study analyses real-world data with a top-down costing approach, reporting patient and body weight-adjusted costs. Simultaneous patient-specific data from the Finnish Prescription Register validated the FVIII consumption data extracted from medical records, showing that the amount of FVIII dispensed from pharmacy did not deviate from the prescribed doses. This finding ensures that our patients and their parents were very adherent to prophylaxis.

The limitations were the retrospective nature of our study, and a relative small sample size. Under-reporting of bleeding frequency is possible, especially in the case of soft tissue or minor bleeds; in addition, the diagnosis of a bleeding event is generally subjective. However, both parents and patients were instructed to report and confirm all joint and other significant bleeds to the hospital; the treatment was guided to be initiated at the hospital and continued at home with a close contact. This clinical practice may diminish the possible impact of under-reporting. It has been shown that the experience of symptoms, positive belief in treatment necessity and good relation with the healthcare provider are motivators for high adherence 503.[23] Thus, by educating and supporting parents and patients, we can improve the adherence for haemophilia treatment and probably also for recording bleeds. All bleeding events were recorded to patients' medical records by a specialist in haemophilia care. At the time of data collection, all data were registered by the same paediatric haematologist, KV, not by local personal, to ascertain coherent data collection across the centres.

The standard deviation of the mean annual treatment costs was wide, representing the variability in treatment intensity and costs between noninhibitor patients vs patients with high-titre inhibitors using high-dose ITI therapy in combination with bypassing clotting agents. The wide distribution of cost data between different studies and even in-between patients in the same study has been found in several previous studies among noninhibitor patients[5]; 472[9]; 455,[6] but especially among inhibitor patients 469[7]; 472[9]; 457.[24] Despite the wide deviation, mean total costs kg^{-1} remained stable during the childhood except in ages 1-3, and 14, when the increment of costs was due to ITI (Figure 2). Higher variation between mean costs per patient and cost increase by age indicates the effect of increasing weight (Figure 1).

At the end of follow-up, patients were relative young (median age, 12.7 years). However, early childhood, in particularly, is the critical treatment period, affecting long-term joint health and quality of life in adulthood. The best long-term joint outcome is achieved starting primary prophylaxis at the earliest age[25-27] even before the first joint bleed compared with the strategy starting secondary prophylaxis after one or more joint bleeds. The number of joint bleeds before starting prophylaxis has a stronger association with the outcome than the age upon starting prophylaxis.[28] In all, with our results of scarce joint bleeds during childhood, we assume good long-term joint health reaching also to adulthood.

The prophylactic FVIII dosing regimen in Finland corresponds to the high-dose Swedish one 458[29]; 499[30]; 462.[31] Although prophylaxis in Finland is implemented mainly via central venous devices, the need for hospitalization was uncommon; costs related to hospitalizations and outpatient visits constituted less than 6% of the total costs beyond 1 year of age. The quality of life was beneficial: regarding joint health and practical prophylaxis via ports at home. In addition, the patient age at home treatment start was low (median, 1.1 years) compared with other western countries; this was 3.3 years in Sweden 455[6] and 4.0 in Denmark 467.[32] As we have reported earlier, long-term CVAD-related complications did not occur, and the incidence of inhibitor development was relatively low (21%) 465[10]; 452.[11] Despite inhibitor development, joint health in inhibitor patients remained good. ITI results were excellent; all patients

(n = 11) who completed ITI achieved tolerance with either complete or partial success.

Although the clinical outcomes are favourable, the high total costs of therapy demand our continued evaluation on how to reduce prophylactic FVIII doses, at least in certain patients. In one-fifth of the cohort, trough levels of FVIII were useful in guiding appropriate prophylactic treatment towards 16% lower annual FVIII consumption. Lower FVIII consumption did not predispose to target joints or arthropathy. We suggest that individualized therapy protects from bleeding complications with cost reductions, but further analyses are warranted.

The development of FVIII-neutralizing antibodies remains the most severe and costly complication of haemophilia therapy. Our results with real-world data are in line with the findings from a recent health economic modelling study, which reported that the lifetime costs of treating adult patients with inhibitors are lower for ITI compared to on-demand or prophylaxis with bypassing agents 457.[24] In our study, after inhibitor detection, direct monthly total costs €/kg quintupled from 259€ to 1473€ mainly due to the use of bypassing agents, corresponding to an annual total cost of 1.3 million € for an average weight (75 kg) adult. During ITI, costs further doubled to 3097€, but after successful ITI, the FVIII consumption of prophylaxis and total costs decreased to the level of noninhibitor patients. The expected payback period estimate of <2 years indicated that, ITI appears cost-neutral (ie, compared to on-demand or prophylaxis with bypassing agents) after a relatively short period: the savings of successful ITI, fully offset the incremental costs due to FVIII used for ITI during the 1.81 years. However, this estimate based on the small number of patients with ITI and should be interpreted with caution. The mean (SD) cost for ITI was 383 448€ (259 085) during early childhood, but it increased ten-fold by age 14 (3 483 120€). Without prospective randomized trial confirming that treatment delay confers benefit, the current practice has been to delay the start of ITI until the inhibitor titre is <10 BU/mL with anticipated enhanced success. In a retrospective study in 2 U.S. haemophilia treatment centres, a titre >10 BU/mL at ITI start did not impact the outcome in subjects with ITI initiation within 1 month of detection 470.[33] Also, health economic consequences emphasize the importance of prompt ITI regardless of the inhibitor titre.

As the use of new extended half-life (EHL) factor concentrates is increasing, our study with reliable data about real-world practices is crucial for the future, to critically compare long-term costs (and potential benefit) between the current and the future treatment options. The data provide relevant information to support decision-making related to new and usually even more expensive treatments, including EHL products, the bispecific antibody recognizing FIX and FX, and gene therapy.

Our earlier results have emphasized the role of early primary prophylaxis via ports to prevent major bleeds and decrease inhibitor incidence 452.[11] Our current study demonstrates that early high-dose prophylaxis provides excellent long-term clinical outcomes. Moreover, rapid ITI therapy during early childhood is successful and seems cost-neutral due to its relatively short expected payback period.

DISCLOSURES

RL has received consultancy or speaker's fee from Bayer, Baxter, NovoNordisk, Octapharma, Pfizer, during the last 5 years, however, not related to this manuscript. PL has got support for attending a symposium from Sobi, Pfizer, Shire and Octapharma. JM is a founding partner of ESiOR Ltd., which carries out health services for pharmaceutical companies and hospitals. The other authors stated that they had no interests which might be perceived as posing a conflict or bias.

AUTHOR CONTRIBUTION

KV, PR and JM designed the research study. KV collected the data and wrote the manuscript. KV, TS and JM performed the statistical analyses and analysed the data. PR, RL and JM contributed to writing of the article. All authors read, edited and approved the final manuscript.

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