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Real-life evidence in evaluating effectiveness of treatment in Haemophilia A with a recombinant FVIII concentrate: A non-interventional study in emerging countries

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Summary. Some progress has been made regarding availability of recombinant factor VIII concentrates and prophylaxis for haemophilia A in emerging countries, where plasma-derived concentrates were used in the vast majority. Clinical studies to document their introduction and effectiveness are so far not widely available in literature. This non-interventional study evaluates the real-life effectiveness and safety of prophylactic and on-demand treatment with recombinant factor VIII formulated with sucrose (rFVIII-FS) for bleed control and preservation of joints in emerging countries from Eastern Europe, North Africa and Middle East area. One hundred and eighty-six patients from 11 countries were enrolled, mean \pm SD age 12.8 ± 12.7 years. At enrolment, majority (79.6%) had severe haemophilia A ($<2\%$ IU mL⁻¹), 47.8% had a target joint, 15% had an inhibitor history and one patient was on immune tolerance induction. During the 24-month observation

period, 58.1% of the patients were prescribed prophylaxis at every visit, 31.7% were on an on-demand regimen. Patients with severe haemophilia A on prophylaxis ($n = 82$) had a mean annual rate of treated bleeds of 2.8 ± 4.4 , whereas it was 19.1 ± 32.0 for the on-demand group ($n = 31$), and a mean total Gilbert Score of 9.9 ± 10.3 at baseline and 4.1 ± 6.7 at study end; vs. 15.2 ± 17.3 and 13.7 ± 17.1 for on-demand respectively. The majority of the bleeds (91.1%) were treated with one or two infusions. Four patients without inhibitor history had a first positive inhibitor test during the study. This study demonstrates the effective use of rFVIII-FS in emerging countries and adds to the established safety profile of rFVIII-FS.

Keywords: clinical study, factor VIII, haemophilia A, prophylaxis

Introduction

The primary goal of treatment for individuals with haemophilia A is to treat and prevent bleeding with intravenous replacement of the deficient clotting factor [1,2]. For individuals with severe bleeding phenotype, early, prophylactic treatment with regular injections of factor VIII (FVIII) is the standard of care in developed countries [1–10]. The availability of recombinant factor VIII (rFVIII) since the 1990s is an important advancement in haemophilia care. After early

plasma-derived products led to transmission of human immunodeficiency and hepatitis viruses in the 1980s, the development of a virus-free source in recombinant FVIII has given more confidence in widespread use of prophylaxis [2]. Recombinant FVIII product formulated with sucrose (rFVIII-FS) has demonstrated efficacy and safety in several studies over the last decade [7,9–14]. After introduction in the USA and Europe, it was one of the first recombinant products made available to some emerging countries, where plasma-derived FVIII were more commonly used [1,15–18]. In developing countries, the availability of effective medications for haemophilia is a major concern and contributes to under-treatment [2,15,16,19,20]. However, availability of recombinant products has increased in recent years [17,19,21] in some countries with improving economy, but few studies are available to

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document their clinical use in such new regions. The EffeKt study (EFFECTiveness and SaFEty of long-term treatment with KogenaTe®Bayer/FS) [22] was conducted to evaluate the effectiveness [23] and safety of long-term treatment with rFVIII-FS for haemophilia A in routine clinical practice in emerging countries from Eastern Europe, North Africa or Middle East area, where rFVIII-FS became available shortly before this study was initiated. As the development of alloantibodies ('inhibitors') to FVIII is a major safety issue in haemophilia A [24,25], information on inhibitor development was also collected systematically.

Materials and methods

Study design

This was a 24-month, prospective, non-interventional study conducted at 51 study centres in 11 countries, between June 2008 and February 2012. It aims to evaluate primarily the effect of prophylaxis and on-demand treatment with rFVIII-FS on bleed rates and joint status in patients with severe and non-severe haemophilia. Socio-economically, the included countries varied mainly from lower- to upper-middle income countries, and their per capita FVIII usage ranged from below 1.0 IU in the majority up to 4.6 in Slovenia [19].

The study received approval from relevant review boards in all countries as required. All treatments had to comply with local product recommendations and the treatment decisions were solely at the discretion of the physician. Patients or their legal guardians provided written informed consent.

Patients

A cohort of patients with severe, as defined with residual factor VIII activity of ≤ 0.02 IU mL⁻¹, and non-severe haemophilia A (0.02 – 0.40 IU mL⁻¹) were consecutively enrolled at clinic visits and afterwards followed up prospectively for 24 months. The ISTH definition [26] of disease severity was not applied, as no Central Laboratory was possible. rFVIII-FS had to be their only source of FVIII (investigator choice). An inhibitor assessment had to be available prior to enrolment. Following patient characteristics were collected on paper case report forms (CRF) by the treating physicians: duration and type of pretreatment, type of regular treatment (Prophylaxis, on-demand or inhibitor-adapted therapy), inhibitor history, target joint [27], concomitant diseases, hepatitis and HIV serostatus.

Effectiveness and safety variables

The following outcomes variables were evaluated per treatment group as available from CRF and patient-

reported infusion diaries at baseline, month 12 and month 24: number and type of annualized treated bleeds (primary endpoint), number, dose and reason for FVIII infusions, IU consumption, joint status measured by the Total Gilbert Score (TGS) and its Physical Examination Score (PES), which does not include the items for bleeds and pain of TGS [28], continuation of rFVIII-FS therapy, assessment of haemostasis during surgeries. For safety, the variables evaluated were general efficacy and tolerability (physician assessment), abnormal laboratory values, inhibitor tests and adverse events (AE) (MedDRA version 15.0) [29] with relation, seriousness, action taken and outcome. Inhibitors were considered serious AE (SAE) due to important medical event.

Testing methodology and statistics

Statistical analysis was descriptive and summary statistics for categorical and quantitative (continuous) variables were used. All analyses were conducted for the non-missing information per specific outcomes variable. Effectiveness outcomes were stratified by haemophilia severity and treatment type. Joint Scores were furthermore stratified by the groups of children (≤ 18 years) and adults (> 18 years).

Treatment regimens were analysed according to the categories 'pure prophylaxis' (PP) and 'pure on-demand' (OD), if patients were prescribed this regimen at every visit. When patients changed regimen within the observation period, they were categorized as 'intermittent prophylaxis'. If inhibitor-adapted therapy was indicated at one visit, the patient was assigned to the ITI group.

The inhibitor status was assessed according to local practice in the respective hospital with the classical [30] or the Nijmegen modified Bethesda assay [31]. Cut-off for low vs. high titre was defined with 5 Bethesda Units (BU) [26]. The outcomes related to infusion reports (IU consumption, infusions and bleedings) were analysed for the patients with available infusion reports and annualized by following formula $[\frac{x}{(\text{last visit date} - \text{enrolment visit date})}] * 365$ days. Due to this annualization methods, Mean and Standard Deviation ($M \pm SD$) are considered more adequate representation of the group and uniformly used for continuous variables, if not otherwise stated. The calculated Annualized Bleed Rate (ABR) covered mainly the number of treated bleeds, as the standard infusion reports did only allow for entry of infusions.

Results

Demographics and baseline characteristics

One hundred and eighty-six patients were enrolled from 51 sites from 11 countries: United Arab Emirates

($n = 8$), Bosnia–Herzegovina ($n = 7$), Croatia ($n = 6$), Israel ($n = 15$), Kazakhstan ($n = 19$), Libya ($n = 9$), Morocco ($n = 6$), Romania ($n = 15$), Russian Federation ($n = 76$), Slovenia ($n = 6$) and Tunisia ($n = 19$). 79.6% ($n = 148$) had severe disease (<0.02 IU mL⁻¹), among them 22.0% ($n = 41$) with residual FVIII activity of 0.01–0.02 IU mL⁻¹ according to local test at diagnosis. 20.4% ($n = 38$) had non-severe haemophilia (>0.02 IU mL⁻¹), among them $n = 14$ with mild disease ($>0.05\%$ IU mL⁻¹). The mean age was 12.8 ± 12.7 years (Median 8.0, range 0–55) with 75.8% (141/186) children (<18 years old). Most were caucasian (81.2%; 151/186). Concomitant disease was reported in 26.3% (49/186) patients at enrolment. A positive serostatus for hepatitis A in 5.9% (11/186), hepatitis B in 17.7% (33/186), hepatitis C in 15.6% (29/186) and HIV in 1.6% (3/186) at baseline were noted. Of those 89 patients with target joints (47.8%), the most common joints were knee (53.9%; 48/89), elbow (47.2%; 42/89) and ankle (38.2%; 34/89) (Table 1).

54.3% (101/186) patients had accumulated over 150 EDs. Majority of 72.6% ($n = 135$) was previously treated with plasma-derived products. Prior to the study, inhibitor assessment in the past was available for 94.1% ($n = 175/186$) patients (11 missing). Fifteen per cent (27/186) had a positive inhibitor history and 11 (5.9%) were still positive at most recent testing (<6 months before enrolment). Three patients with inhibitor history had undergone ITI and one patient with a high titre was still undergoing ITI at the time of enrolment. The regular mode of therapy with FVIII products was prophylaxis for 60.2% (112/186) of patients. Prophylaxis was once weekly in 9/186 patients (4.8%), 43 patients twice weekly (23.1%) and 60 patients (32.3%) with 3 weekly injections at start of the study. Mean age of those on prophylaxis vs. on-demand was similar, 12.7 ± 12.5 and 14.6 ± 14.0 respectively. However, recruited patients with severe haemophilia had a higher mean age (13.8 ± 13.6 years) than those with non-severe haemophilia (8.8 ± 7.9) – the latter included only two adults (Table 1).

Study period: disposition

The mean length of the observation period was 731 ± 256 days. One hundred and three patients (55.4%) had started rFVIII-FS treatment prior to enrolment, the rest at enrolment. During the study, 58.1% (108/186) of the patients were prescribed prophylaxis at every visit as indicated by the physician – similar proportion for severe and non-severe (Table 2). The mean prescribed dose per prophylaxis injection was 26.7 ± 11.7 IU/kg. Information on self-infusion or home treatment was not collected in the CRF.

Outcomes derived from patient-recorded infusion reports

Infusion reports were available for 83.3% (155/186) of the patients. A mean ABR of 2.8 ± 4.5 total bleeds and a mean of 1.4 ± 3.2 joint bleeds were calculated for the severe haemophilic group on PP with available infusion reports ($n = 82$). The mean ABR for OD was higher with 19.1 ± 32.2 and 4.1 ± 11.6 joint bleeds in patients with severe haemophilia ($n = 39$). (Patients with <0.01 IU mL⁻¹ FVIII activity had a similar ABR of 3.1 ± 5.0 and 22.8 ± 35.8 respectively). The difference in ABR between PP and OD was less pronounced in the subgroup of non-severe haemophilia (Fig. 1).

For the whole study period from 0 to 24 months, a mean of 124 ± 115 EDs was documented. Patients receiving PP had a mean of 164 ± 121 EDs compared to 39 ± 43 EDs for patients receiving OD.

A total of 19 445 injections were recorded. Most were given for regular prophylaxis ($n = 16 179$; 83.2%), followed by injections for bleeds ($n = 2373$; 12.2%); the remainder of injections were given for special prophylaxis during periods of increased physical activity (2.6%), surgeries (0.4%), recovery testing (1.6%) or other reasons (5.1%). The most common bleeding site was 'joint' (57%). Most bleeding events (91.1%) were treated with one or two infusions.

Mean annual doses were $2128 + 2627.5$ IU kg⁻¹ for severe and $1573.3 + 1506.7$ IU kg⁻¹ for non-severe haemophilia. The mean actual dose per prophylaxis injection (27 ± 11 IU kg⁻¹) was similar to the prescribed dose mentioned above (26.7 ± 11.7 IU kg⁻¹). Actual weekly dose was 43.4 ± 35.9 IU kg⁻¹. OD had a lower yearly consumption (1174 ± 3415 IU kg⁻¹) than PP (2492 ± 2034 IU kg⁻¹) (Table 3).

Joint assessments

Gilbert scores (GS) were available for 116 patients (62.4%). Patients with severe haemophilia on PP had mean TGS of 9.9 ± 10.3 at Baseline and 4.1 ± 6.7 at last measurement, whereas the scores were higher for OD with 15.2 ± 17.3 and 13.7 ± 17.1 respectively. Respective mean PES for PP was 6.7 ± 7.82 at baseline and 3.3 ± 6.0 at last measurement and here also higher for OD with $15.2 + 17.3$ and $13.7 + 17.1$ respectively. A cross-stratification by age and by treatment group is illustrated in [Figs 2 & 3] for severe haemophilia and shows lower scores for children ($M < 10$) than adults ($M \geq 10$) and a smaller variance for PP than OD. The few available data for intermittent prophylaxis and non-severe haemophilia are explained in [Figs 2 & 3].

Table 1. Baseline demographic characteristics.

	Severe with 0–2% IU ml ⁻¹ (n = 148) (79%)	Non-severe (>2% IU ml ⁻¹) (n = 38) (21%)	Total (N = 186) (100%)
Age, Mean ± SD (range), year	13.8 ± 13.6 (0–55)	8.8 ± 7.94 (1–36)	12.8 ± 12.7 (0–55)
Age category, n (%)			
< 2 year	21 (14.2)	2 (5.3)	23 (12.4)
≥2 to ≤6 year	45 (30.4)	17 (44.7)	62 (33.3)
>6 to ≤12 year	20 (13.5)	9 (23.7)	29 (15.6)
>12 to ≤18 year	19 (12.8)	8 (21.1)	27 (14.5)
>18 to ≤40 year	34 (23.0)	2 (5.3)	36 (19.4)
>40 to ≤65 year	9 (6.1)	0 (0.0)	9 (4.8)
Weight, Mean ± SD in kg	39.9 ± 26.0	33.5 ± 22.2	38.5 ± 25.3
Race, n (%)			
White	123 (83.1)	28 (73.7)	151 (81.2)
Black	4 (2.7)	0	4 (2.2)
Asian	7 (4.7)	3 (7.9)	10 (5.4)
Other	10 (6.8)	1 (2.6)	11 (5.9)
Missing	4 (2.7)	6 (15.8)	10 (5.4)
Presence of target joint n/N (%)	79/148 (53.4%)	10/38 (26.3)	89/186 (47.8)
Age ≤18 years	43/105 (41%)	8/36 (22.2%)	51/141 (36.2%)
Age >18 years	36/43 (83.7%)	2/2 (100%)	38/45 (84.4%)
On-demand at baseline	30/44 (68.2%)	7/15 (46.7%)	37/59 (62.7%)
Prophylaxis at baseline	44/88 (50%)	3/20 (15%)	47/108 (43.5%)
Product used in the past:			
Recombinant FVIII	38 (25.7%)	7 (18.4%)	45 (24.2%)
rFVIII-FS	25	5	30
FL-rFVIII	12	2	14
BDD-rFVIII	3	0	3
Plasma-derived FVIII*	106 (71.6%)	29 (76.3%)	135 (72.6%)
Bypassing agents†	3	0	3
Unknown/missing/none	3	2	5
N with positive inhibitor tests in medical history (high titre; low titre) n (%)	24 (16.2%) (11;12, 1 missing)	3 (7.9%) (0;3)	27 (14.5%) (11;16; 1 missing)*
N with last inhibitor test positive before enrolment‡ (high titre; low titre) n (%)	10 (6.8%) (5;5)	1 (2.6%) (0;1)	11 (5.9%) (5;6)
ED at baseline§ (n)			
0	2 (1.4%)	1 (2.6%)	3 (1.6%)
1–4	1 (0.7%)	1 (2.6%)	2 (1.1%)
5–20	12 (8.1%)	3 (7.9%)	15 (8.1%)
21–75	15 (10.1%)	6 (15.8%)	21 (11.3%)
76–150	38 (25.7%)	6 (15.8%)	44 (23.7%)
>150	80 (54.1%)	21 (55.3%)	101 (54.3%)
Concomitant diseases			
None	102 (68.9%)	35 (92.1%)	137 (73.7%)
Most common:	8 (5.4%)	2 (5.3%)	10 (5.4%)
-Gastrointestinal	6 (4.1%)	0	6 (3.2%)
-Hepato-Biliary	11 (7.4%)	0	11 (5.9%)
-Infections	9 (6.1%)	0	9 (4.8%)
-Musculoskeletal			

*Plasma-derived products: Majority was Haemoctin (n = 24), Immunate (n = 40) and Octanate (n = 42), rest: Cryoprecipitate, Emoclot, Factane, Fresh Frozen Plasma, Haemofil M, Koate-DVI, Unknown (n = 2–9). Multiple answers possible.

†Bypassing agents: APCC (n = 1) or rFVIIa (n = 2).

‡Within <6 months prior to enrolment.

§The number of EDs is an estimate by the physician: only the number behind an operator in the CRF item (e.g. < or >) has been used for this categorization.

rFVIII-FS = recombinant factor VIII formulated with sucrose (Kogenate® Bayer/FS or Helixate® NexGen/FS), FL-rFVIII = full-length recombinant factor VIII (Recombinate®), BDD-rFVIII = B-domain-deleted recombinant factor VIII (ReFacto®).

Safety analysis

Over the 24-month observation period, at least one AE was reported for 31 patients (16.7%). Eleven patients (5.9%) had 34 non-serious AEs and 20 patients (10.8%) had 40 SAEs. The majority of AEs

were in the organ system class of ‘infections and infestations’, mainly respiratory and gastrointestinal; and one patient with non-drug-related sepsis that resolved during the study. No drug-related infections were reported during the study. Two patients (1.1%) died

Table 2. Number of patients *n* (%) by regular treatment regimen during the study.

	Severe (<i>n</i> = 148)	Non-severe (<i>n</i> = 38)	Total (<i>N</i> = 186)
PP*	88 (59.5)	20 (52.6)	108 (58.1)
Intermittent prophylaxis†	13 (8.8)	2 (5.3)	15 (8.1)
OD‡	44 (29.7)	15 (39.5)	59 (31.7)
ITI	3 (2.0)	1 (2.6)	4 (2.2)

*Pure Prophylaxis: prescribed prophylaxis indicated at each available visit BL, M12, M24.

†Intermittent prophylaxis: switched between prophylaxis and on-demand during the study.

‡On-demand: treated only on-demand for bleed resolution throughout the study.

ITI = Immune tolerance Induction or inhibitor-adapted therapy.

for non-drug-related reasons: one patient with severe haemophilia treated OD died from the consequences of an intracerebral haematoma at age 22 years, without inhibitor, but previously treated with rFVIIa. Another patient with severe haemophilia, 38 years old, died due to respiratory failure, HIV and HBV positive, and was suffering from Staphylococcus Aureus pneumonia, treated OD.

13.4% (25/186) patients discontinued rFVIII-FS therapy. Overall, the primary reasons for dropouts were unavailability of rFVIII-FS or budget constraints (15/25; nine due to political instability in Libya). Apart from the two deaths mentioned, three patients had to discontinue due to AE/insufficient efficacy: one severe patient on ITI left 17 months after enrolment, another one developed an inhibitor, and a third patient discontinued after 8 months due to a non-serious,

non-drug-related acute respiratory infection. Five additional patients were lost to follow-up.

All nine patients with drug-related SAEs during the study were inhibitors; measured by classical Bethesda assays. For five of these nine patients, inhibitor activity was recurrent or persistent, i.e. positive prior to enrolment (three cases on ITI). Remaining four had a first positive result during the observation period and classified as *de novo* inhibitors. As two of the five recurrent inhibitors had developed before study start on rFVIII-FS, the number of *de novo* inhibitor patients with rFVIII-FS would conservatively be estimated as 6 among 85 patients with < 150 ED (7%). Four of these six patients had ethnicity indicated as 'other', five of these six patients had severe haemophilia A. Among the 20 patients with < 20 EDs at baseline (Table 1), none had a positive inhibitor tested during the study. Details of persistent, recurrent and *de novo* inhibitors are listed in (Table 4).

Physician global assessment of rFVIII-FS effectiveness and tolerability was good/excellent for 160 of 171 patients (93.6%) and 164 of 171 (95.3%) with available assessment respectively. Effectiveness and tolerability was assessed insufficient in five patients (2.9%) and four patients (2.3%) respectively; two with documented inhibitors during the study.

During the 24-month study period, 18 surgeries were performed on 15 patients. The surgeries ranged from minor (tooth extraction) to major (intracerebral haematoma). Haemostasis in all surgeries was ranked as good/excellent by estimate of the treating physician, except one where the rating was missing.

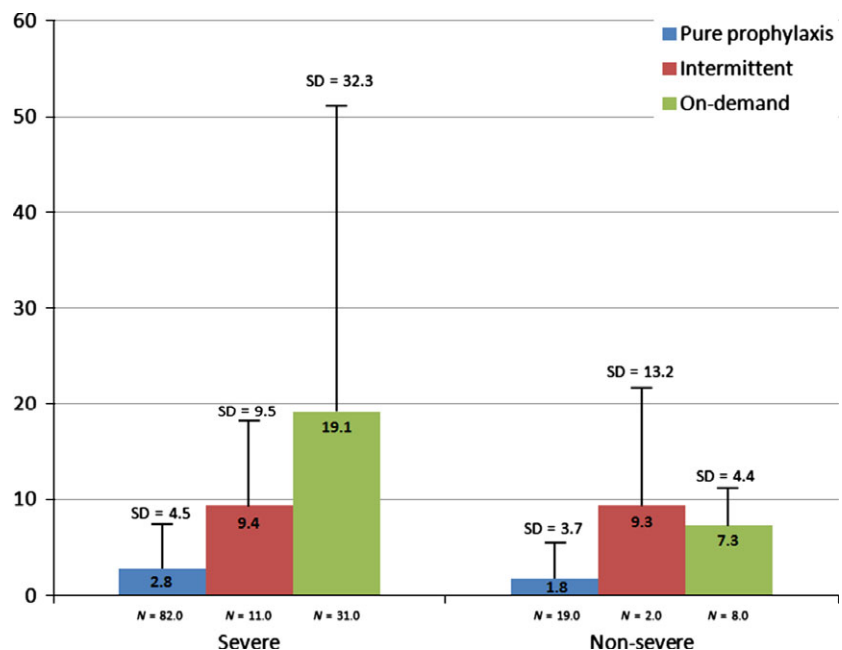


Fig. 1. Annualized number of treated bleed rate per patient (ABR) for patients with severe and non-severe haemophilia A receiving rFVIII-FS pure prophylaxis, intermittent prophylaxis or pure on-demand treatment. End of the bar and data labels represent mean values; whiskers denote standard deviation values. The median (Q1–Q3) values for prophylaxis were 0 (0–3.7) and 0.5 (0–2.0) for severe and non-severe patient group respectively. For on-demand treatment, they were Median = 12 (4.5–20.6) and Median = 6.6 (5.5–10.0) for severe and non-severe patient group respectively.

Table 3. Annualized FVIII-FS consumption in IU kg⁻¹ per patient (based on available infusion reports*, *n* = 155).

	Severe (<i>n</i> = 148)	Non-severe (<i>n</i> = 38)	Total (<i>n</i> = 186)
All			
<i>n</i> with available infusion reports	125	30	155
Mean (M) ± Standard deviation (SD)	2129 ± 2628	1573 ± 1507	2021 ± 2457
Median (Q1–Q3)	1311 (304–2991)	820 (369–2972)	1238 (304–2991)
Pure prophylaxis			
<i>n</i> with available infusion reports	82	19	101
M ± SD	2599 ± 2104	2039 ± 1674	2493 ± 2034
Median (Q1–Q3)	2405 (719–4100)	2131 (392–3507)	2352 (664–3923)
Intermittent prophylaxis			
<i>n</i> with available infusion reports	11	2	13
M ± SD	965 ± 771	1097 and 1716 [†]	1033 ± 734
Median (Q1–Q3)	963 (303–1311)	1097 and 1716 [†]	1024 (311–1311)
On-demand			
<i>n</i> with available infusion reports	31	8	39
M ± SD	1357 ± 3816	465 ± 390	1174 ± 3415
Median (Q1–Q3)	370 (243–676)	418 (204–509)	370 (243–622)
Missing	23	8	31

*Information on injections from patient diaries has been used to calculate the average values per year according to the formula: (number of infusions or bleeds: time in days documented in patient diary) × 365 (= Annualization).

[†]These values are the specific values of the two patients.

Two patients with ITI had infusion reports available, one patient with severe (331 IU kg⁻¹ per year) and one with non-severe haemophilia (1930 IU kg⁻¹ per year); their infusion reports appeared inconsistent. ITI = Immune tolerance induction or inhibitor-adapted therapy.

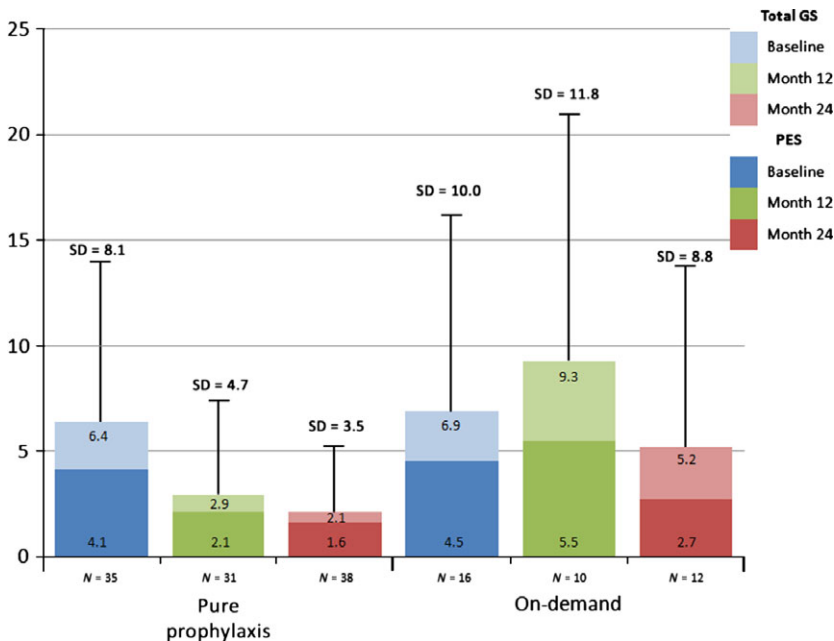


Fig. 2. Children’s (<18 years) Joint status as assessed via Total Gilbert scores (GS) and Physical Examination Scores (PES) for patients with severe haemophilia at baseline, Month 12 and Month 24 per treatment strategy (pure prophylaxis vs. on-demand). In the light coloured bars, end of the bar and data labels represent mean values of TGS: whiskers denote standard deviation values. In the dark coloured bars, end of the bar and data labels represent mean values of PES. In the intermittent prophylaxis group, mean values of TGS of 10 paediatric patients with severe haemophilia were 5.3 ± 7.9, 2.9 ± 3.1 and 2.8 ± 2.9 at baseline, month 12 and month 24 respectively. Mean TGS and PES of 18 children with non-severe haemophilia was 0.0 for all visits and treatment groups (Maximum value reached was 3).

Discussion

This 24-month observational study describes the use of regular therapy with rFVIII-FS for OD bleeding control and for prophylaxis to prevent bleeds and preserve the joint status in recruited patients with mainly severe haemophilia A (< 0.02 IU mL⁻¹) from emerging countries in North Africa, the Middle East area and Eastern Europe.

Patients’ ABR with prophylaxis was low, and they maintained their joint status with an efficacy and

safety profile consistent with that previously reported in the literature [10–13,32–35]. rFVIII-FS was administered as prophylactic treatment in ~55% of the total sample with 2–3 times per week, and in <5% with 1 × per week. ABRs on prophylaxis vs. on-demand group were comparable to other clinical studies [7,8,10,13,33,36] with 3 × weekly injections for severe haemophilia. The interventional Joint Outcomes Study [7] had a mean ABR of 1.2 on the prophylaxis arm vs. 17.1 in the OD arm. However, the ABR in our study seems relatively low in both groups

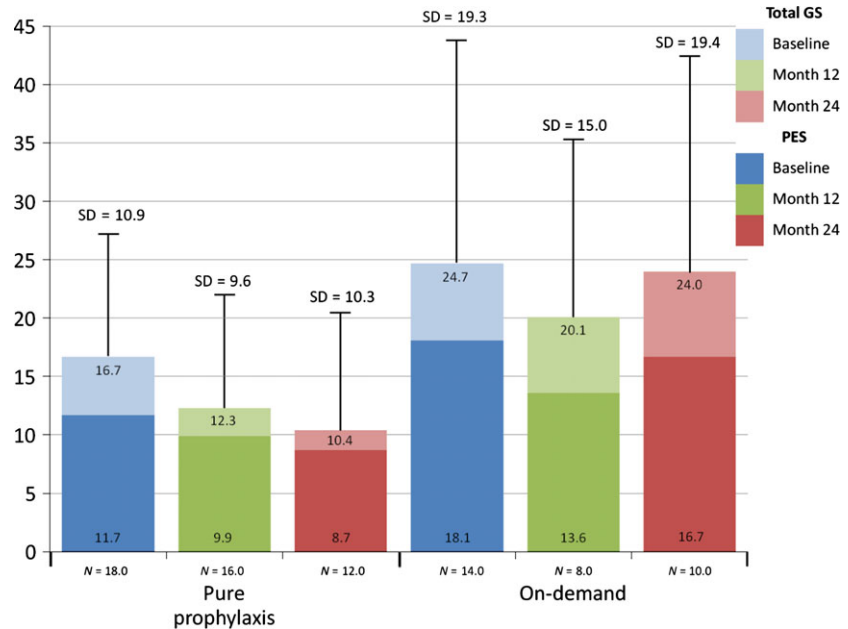


Fig. 3. Adults' (>18 years) Joint status as assessed via Gilbert scores (GS) for patients with severe haemophilia at baseline, Month 12 and Month 24 per treatment strategy. In the light coloured bars, end of the bar and data labels represent mean values of TGS; whiskers denote standard deviation values. In the dark coloured bars, end of the bar and data labels represent mean values of PES. For adults, TGS of only n = 2 patients with severe haemophilia were available (mean values 8.5 ± 12.0, 12.5 ± 3.5, 11.5 ± 2.1 at baseline, month 12 and month 24 respectively). No GS were available for adult patients with non-severe haemophilia.

Table 4. Characteristics of the patients with recurrent/persistent or first positive inhibitor test (de novo) during the study.

Race	ED at BL	Age at BL	Inhibitor hx	Haemophilia severity	Peak level (a)	First level (a)	Last level (a)	Tx per visit BL/12M/24M	Type of inhibitor classification
Other	>100	5	No	Severe	(b)	-	-	P/P/P	De novo
Other	>50	1	Yes	Severe	19	19	3	P/P/P	Recurrent/de novo (d)
Other	25	1	No	Severe	14	3	2	OD/ITI/ITI	De novo
Other	12	1	Yes	Severe	>1	>1	0	ITI/ITI/P	Persistent/de novo (d)
White	<100	2	No	Severe	102	>40	100	OD (e)	De novo
White	60	0.6	Yes	Severe	1027	852.6	57.6	P/ITI/ITI	Recurrent
White	1095	3	(C)	Moderate (2-5%)	(b)	-	-	P/ITI/P	Recurrent
White	386	7	Yes	Moderate (2-5%)	1	0	0	P/P/P	Recurrent
White	78	2	No	Moderate (2-5%)	2.1	0	0.9	P/P/P	De novo

a = Inhibitor test result as measured during the observation period, peak/first/last level = highest/first/last level measured; b = Inhibitor was reported as adverse event without specification of inhibitor titre test result; c = For this patient, a positive inhibitor test prior to enrolment was available, but the investigator did not label this as positive inhibitor history in the CRF item; d = Always treated with rFVIII-FS prior to study start, therefore assigned to de novo category. e = Patient discontinued in the study after occurrence of the inhibitor at 0 ED after study entry.

ED = Exposure Days to FVIII, BL = Baseline, hx = history; tx = treatment, 12M = 12 month visit, 24M = 24 months visit

for a non-interventional study [13,14,37], as maybe only major bleeds were treated or recorded, especially when on prophylaxis treatment.

Joint scores for children with severe haemophilia were generally lower (TGS<10 points) than for adults (TGS>10), representing the unaffected joint status in young age. However, some target joints and affected joints were present already in some children with severe haemophilia, as known from other studies [7]. Average scores at study end were one or two points lower than at baseline in children on prophylaxis with a smaller variance than for OD. Whether this is a meaningful difference cannot be determined with the study design. Those adults who were already on prophylaxis before study start showed better mean joint scores (16 ± 11) than on-demand (24 ± 19) at baseline, both groups with a broad variance. Information on prior prophylaxis was not collected. While the

average TGS for prophylaxis were seven points lower at study end, the average PES scores representing the musculoskeletal status only differed by two points at study end for adults; see also Collins *et al.* 2010 [9]. The average values for adult OD patients did not change and remained always on a higher level with a larger variation compared to prophylaxis, as seen also in other studies [9,38].

The safety profile was as expected in haemophilia A and for the observed age groups. The study would result in a conservatively estimated de novo inhibitor rate of 7% (95%-CI 3-15%) in those patients with <150 EDs (n = 6/85). However, as this sample comprises non-severe and severe haemophilia and most of them previously treated (>20 ED), this result cannot be compared to results from recent PUP studies with rFVIII-FS [25,39-45]. No patient with <20 EDs (n = 20) at study inclusion tested positive for

inhibitors during the study, yet only three patients had 0 ED at baseline. PTP patients (with >150 EDs) showed no *de novo* development of inhibitors in this study.

While this observational, international study on the use of recombinant factor products in emerging countries provides a wealth of information and adds important evidence out of real-life, some limitations need to be taken into account when drawing conclusions from this study: (i) Infusion reports and Gilbert Scores were not available for all patients, which leaves smaller number of patients in the stratified groups for comparisons. (ii) The study cannot describe the extent of recombinant product use and prophylaxis in these countries in general, as subjects were consecutively recruited in comprehensive haemophilia treatment centres in major cities only. This set-up implied also that non-severe patients are not representative of their population, as those with severe bleeding phenotype attending the clinic more often had a higher chance to be recruited, which is obvious from the PP proportion of non-severe patients. (iii) The data from 51 sites from the 11 participating countries appear heterogeneous according to classification by World Bank criteria and IU per capita [19]. Although 50% of prophylaxis patients had <2500 annual IU consumption in this study, there were also ~25% of patients with more than 3500 IU per year as is the standard in some developed countries [16]. On the other side, some countries suffered from lack of resources and political instability, which also led to discontinuations. (iv) The low number of available FVIII recovery and inhibitor tests as well as some issues with diagnostic accuracy of moderate patients (0.01–0.02 IU mL⁻¹) suggests an issue with availability of assays [46]; mainly one-stage assays were applied; without central laboratory and genetic testing. Exact number of EDs until onset of inhibitor or prior inhibitor history was difficult to determine due to the infrequent testing and the vague estimate of prior ED.

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Conclusion

Early assessment, prophylactic treatment and preventative therapy for musculoskeletal complications are a current goal in developed countries. However, developing countries often were limited to on-demand therapy, therapy for invasive procedures and rehabilitative therapy [16]. This study shows the effectiveness of long-term treatment with rFVIII-FS and that prophylaxis is possible in specific emerging countries from Eastern Europe, North Africa and Middle East Area. rFVIII-FS is effective and safe in those patients on treatment. Even though this is a non-interventional study, the descriptive findings align with available evidence on effectiveness of prophylaxis from previous studies in developed as well as developing countries with FVIII products. Collection via paper-based forms and the regulatory processes have required many efforts, but the amount of non-missing information should encourage further studies in this area.

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