

Secondary prophylaxis with recombinant activated factor VII improves health-related quality of life of haemophilia patients with inhibitors

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Summary. Haemophilia patients with inhibitors characteristically have impaired joint function and reduced health-related quality of life (HRQoL). This analysis examined whether secondary prophylaxis with recombinant activated factor VII (rFVIIa) improves HRQoL vs. conventional on-demand therapy in patients with haemophilia with inhibitors and frequent bleeds. After a 3-month preprophylaxis period, 22 patients received daily rFVIIa prophylaxis (90 or 270 µg kg⁻¹) for 3 months, followed by 3 months' postprophylaxis. Days of hospitalization, absence from school/work and mobility aids requirements were recorded. HRQoL was assessed by EuroQoL (EQ-5D) questionnaire, visual analogue scale (VAS), derived Time to Trade-Off (TTO) scores and Quality Adjusted Life Years (QALYs). rFVIIa prophylaxis significantly ($P < 0.0001$) reduced bleeding frequency vs. prior on-demand therapy. Hospitalization (5.9% vs. 13.5%; $P = 0.0026$) and absenteeism from school/work (16.7% vs. 38.7%;

$P = 0.0127$) decreased during prophylaxis; these effects tended to be maintained during postprophylaxis. HRQoL (evaluated by EQ-5D) tended to improve during and after rFVIIa prophylaxis. Notably, pain decreased and mobility increased in 40.9% and 27.3% of patients, respectively, at the end of the postprophylaxis period vs. preprophylaxis. Median VAS score increased from 66 to 73 ($P = 0.048$), and TTO scores suggested better HRQoL (0.62 vs. 0.76; $P = 0.054$) during postprophylaxis than preprophylaxis. Small to moderate changes in effect sizes were reported for VAS and TTO scores. Median QALYs were 0.68 (VAS) and 0.73 (TTO). Reductions in bleeding frequency with secondary rFVIIa prophylaxis were associated with improved HRQoL vs. on-demand therapy.

Keywords: haemophilia, HRQoL, inhibitors, recombinant activated factor VII, secondary prophylaxis

Introduction

Patients with haemophilia and inhibitors often develop severe bleeding complications such as

The participating institutions and investigators are listed in the Appendix.

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multiple joint, muscle and deep tissue bleeds [1]. Recurrent bleeding in the joints results in progressive deterioration of the cartilage and subchondral tissue [2]. This, in turn, can cause severe pain and debilitating arthropathy, leading to permanent disability and significant impairment of health-related quality of life (HRQoL) [3,4].

The burden of extensive bleeding and orthopaedic complications, and their impact on HRQoL, is more severe in inhibitor than in non-inhibitor patients [5–7]. Inhibitor patients typically spend a higher number of days in hospital or absent from school or employment, and have a greater requirement for

mobility aids, which can have a pronounced psychosocial impact on their wellbeing [8]. Thus, management of haemophilia patients with inhibitors to prevent joint bleeds and arthropathy, and thereby improve their perceived HRQoL, remains a key clinical challenge.

Prophylaxis in non-inhibitor patients has been shown to be effective in reducing bleeding frequency and hospitalization/absenteeism from school or work vs. conventional on-demand therapy [9–13]. Evidence for secondary prophylaxis in inhibitor patients is more limited. Individual case reports and observational studies have documented reduced bleeding and improved HRQoL with recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC) prophylaxis compared with on-demand therapy [14–21], suggesting that secondary prophylaxis may be a promising treatment for inhibitor patients. The potential for this approach has recently been substantiated by the first prospective, multicentre, randomized, double-blind trial of secondary prophylaxis with rFVIIa in inhibitor patients with frequent bleeds [22]. The results demonstrated that secondary rFVIIa prophylaxis (90 or 270 $\mu\text{g kg}^{-1}$) given once daily for 3 months resulted in clinically significant reductions in bleeding frequency vs. on-demand therapy, without compromising safety. Notably, the majority of the decrease in bleeding was maintained during a subsequent 3-month postprophylaxis period [22].

This is the first study to explore the possible benefits of a prophylactic dose regimen in haemophilia patients with inhibitors vs. on-demand therapy. The goal was to determine if the reduction in bleeding frequency with secondary rFVIIa prophylaxis reported by Konkle *et al.* [22] was associated with improved HRQoL vs. treatment on demand in this clinical trial setting. Patient HRQoL was evaluated by time spent in hospital and absence from school or work, and by the validated, 5-dimensional EuroQoL (EQ-5D) questionnaire, assessment of general health on the EQ-5D visual analogue scale (VAS), and from Quality Adjusted Life Years (QALYs) and EQ-5D Time to Trade-Off (TTO) scores.

Materials and methods

Patients and trial design

Full details of this prospective, double-blind, parallel-group trial have been reported previously [22]. Briefly, patients with congenital haemophilia A or B with inhibitors were evaluated over a 3-month

preprophylaxis (observation) period. Patients with frequent bleeds (mean \geq four bleeds/month) were then randomized to receive 90 or 270 $\mu\text{g kg}^{-1}$ rFVIIa (NovoSeven[®], Novo Nordisk A/S, Bagsværd, Denmark) intravenously once daily for 3 months [prophylaxis (treatment) period], followed by 3 months' postprophylaxis. Patients were treated on-demand for bleeds during the pre- and postprophylaxis periods. Number of bleeds per month was recorded throughout the trial.

Of the 38 patients recruited to the trial, 37 entered the preprophylaxis period [22]. All patients treated with rFVIIa (21 [95.5%] haemophilia A; 1 [4.5%] haemophilia B) completed the trial. No major differences in baseline characteristics or demographics were observed between treatment groups (90 and 270 $\mu\text{g kg}^{-1}$ rFVIIa). Median (range) age was 13.0 (5.1–50.5) and 17.8 (10.6–56.1) years, respectively, and 91% and 100% of patients had target joints [22].

HRQoL and health economic endpoints

Health-related quality of life was evaluated at screening and at the end of the preprophylaxis, prophylaxis and postprophylaxis periods. HRQoL data were not available for two patients at the visit at the end of the prophylaxis period. Changes in the following patient health economic endpoints were recorded: days of hospitalization related to bleeds; days unable to attend school or work and days requiring mobility aids (e.g. wheelchair, crutches, cane).

In addition, HRQoL was determined via the self-administered EQ-5D questionnaire. This method was chosen as it is a validated, generic questionnaire widely used in health economic calculations [23], and because no validated, haemophilia-specific HRQoL questionnaire was available at the trial onset. The five dimensions of the EQ-5D health profile assess mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with three levels of severity: 'no problems (NP)', 'moderate problems (MP)' and 'severe problems (SP)' [23]. Patients also rated their general health using the VAS, where 0 and 100 are the worst and best imaginable health status respectively [24]. The VAS has previously been shown to be a reliable and valid tool for assessing HRQoL in haemophilia patients with and without inhibitors [25].

Results from the EQ-5D profile and VAS score were converted to a EQ-5D TTO score using UK-population-based preference weights [24]. The UK was selected as our comparator population as this is the most frequently used weighting and because of

the fact that this was a multinational study. The lower the TTO score, the lower the preference for being in a specific health state (1 = perfect health; 0 = death; negative scores = health states considered worse than death). Effect sizes were estimated as mean absolute change of score/standard deviation at baseline [26] to determine clinical importance of the differences between visits.

QALYs

Quality adjusted life years were computed using the following equation for each patient and correspond to the time spent in the different states combining scores (VAS or TTO score) and associated time windows; for this purpose, VAS scores were normalized (e.g. divided by 100), to have scores ranging from 0 to 1, e.g.:

$$\text{QALYs} = 90 \times 0.5 \left[(\text{Score}_{\text{at start of prophylaxis}} + \text{Score}_{\text{at end of prophylaxis}} + (\text{Score}_{\text{at end of prophylaxis}} + \text{Score}_{\text{at end of postprophylaxis}})) / 180 \right]$$

The advantage of using a QALY as a measure of health outcomes is that it simultaneously captures gains from reduced morbidity (quality gains) and reduced mortality (quantity gains) and combines these into a single measure. Calculation of QALYs requires two types of data. First, the path of health states and duration of each health state over the time span for which the QALYs are to be calculated. Ideally, duration would be based on life expectancy. However, calculations can also be based on clinical trials, if we assume that health state changes between measurements are smooth and gradual over time, so that changes in TTO scores can be approximated by a straight line. Secondly, preference weights, derived from TTO measurements on a random sample of the general public [27], are required for the health states for the same durations.

By using both the VAS and TTO scores, the utility weights could be based on preference, measured on an interval scale, and anchored on life and death. In addition, VAS is easy to understand and produces values that are sensitive to changes in health states. TTO scores were chosen because strength of preference is generally defined in terms of trade-offs, and thus TTO elicits preferences for different health states by requiring trade-off between quantity and quality of life.

Statistical analysis

The statistical analyses were performed on the intention-to-treat population, defined as all patients randomized and exposed to at least one dose of rFVIIa [22]. The study aimed to compare rFVIIa prophylaxis vs. on-demand therapy, and therefore all patients were evaluated together, irrespective of rFVIIa dose, for this analysis. As participation in the trial alone could have influenced patient HRQoL, the randomization visit (after preprophylaxis) was considered more appropriate than the earlier screening visit for comparing HRQoL prior to prophylaxis with subsequent visits. *P*-values <0.05 were considered significant.

Changes in the number of bleeds between trial periods were analysed by logistic regression, with the log of the ratio between period lengths included as an offset, and by Wald's test.

Rates for hospitalization, days off school or off work, and requirements for mobility aids during each trial period for all patients, and the absolute change between periods, were summarized using simple statistics (sign test of combined treatment groups). Changes in severity of each EQ-5D dimension after preprophylaxis to later visits were assessed using shift tables. Changes in VAS and TTO scores were assessed by median difference and Wilcoxon rank sum test and correlations between the mean number of bleeds per month per trial period and HRQoL (mean VAS and mean TTO score at the end of each trial period) were assessed using Pearson's correlation test as exploratory analyses. TTO scores with a UK conversion and QALYs for on-demand rFVIIa treatment have been reported previously for haemophilia patients with inhibitors [8,28,29].

Results

Efficacy and safety

During the trial 821 bleeds were reported, of which 558 were spontaneous episodes. Most of the bleeds (*n* = 440) were into target joints. In addition, there were 161 joint bleeds and 220 bleeds at other sites. rFVIIa prophylaxis (90 or 270 µg kg⁻¹) significantly (*P* < 0.0001) decreased the mean number of bleeding episodes per month vs. on-demand therapy during the preprophylaxis period (Table 1) [22]. This reduction persisted during the 3-month postprophylaxis period (Table 1). No safety concerns, including no thromboembolic adverse events, occurred during the study [22].

Table 1. Number of bleeding episodes per month during the preprophylaxis, prophylaxis and postprophylaxis periods.

Trial period	Number of bleeds	90 µg kg ⁻¹ rFVIIa (<i>n</i> = 11)	270 µg kg ⁻¹ rFVIIa (<i>n</i> = 11)	Total (<i>n</i> = 22)
Preprophylaxis	Total	212	196	408
	Mean (SD)/month	5.6 (1.7)	5.3 (1.9)	5.5 (1.8)
Prophylaxis	Total	106	75	181
	Mean (SD)/month	3.0 (1.8)**	2.2 (1.7)**	2.6 (1.8)**
Postprophylaxis	Total	137	95	232
	Mean (SD)/month	4.1 (2.4)*, †	2.7 (1.5)**	3.4 (2.1)**, ††

n = number of patients.

P* < 0.01, *P* < 0.0001 vs. preprophylaxis period; †*P* < 0.05, ††*P* < 0.01 vs. prophylaxis period.

HRQoL

Prophylaxis with rFVIIa more than halved the proportion of days in hospital attributable to bleeding vs. on-demand therapy during the preprophylaxis period (*P* = 0.0026; Fig. 1a). The median number of days of bleeding-related hospitalization decreased from 9.5 to 1.5 days in 3 months. There were non-significant trends towards the effect of rFVIIa prophylaxis being maintained during the postprophylaxis period, with median hospitalization rates of 16%, 11% and 9% during the preprophylaxis, prophylaxis and postprophylaxis periods respectively.

The proportion of days absent from school or work (Fig. 1b) was also significantly less (*P* = 0.0127) during rFVIIa prophylaxis than the preprophylaxis period (38.7% vs. 16.7%). The median number (rates) of absentee days from school/work decreased from 18.5 days (19%) during the preprophylaxis period to 4.5 days (5%) with

rFVIIa prophylaxis and 8.5 days (11%) during postprophylaxis.

Overall use of mobility aids remained unchanged throughout the trial, with patients requiring mobility aids on 28.3%, 27.5% and 26.2% of days in the preprophylaxis, prophylaxis and postprophylaxis periods respectively.

EQ-5D and TTO score

Evaluation of the EQ-5D health profile revealed a trend for improvements in HRQoL, most notably in the pain and mobility domains, at the end of rFVIIa prophylaxis and postprophylaxis periods compared with the preprophylaxis period (Fig. 2).

At the end of 3 months' prophylaxis with rFVIIa, there was a considerable shift towards improvements in pain outcome, with 35% (7/20) of patients with moderate or serious problems reporting a reduction in pain vs. on-demand therapy received during preprophylaxis. In addition, 5% (*n* = 1) of patients remained with no pain or discomfort. Three months later, at the end of the postprophylaxis period, pain was decreased in 40.9% (9/22) of the patients with

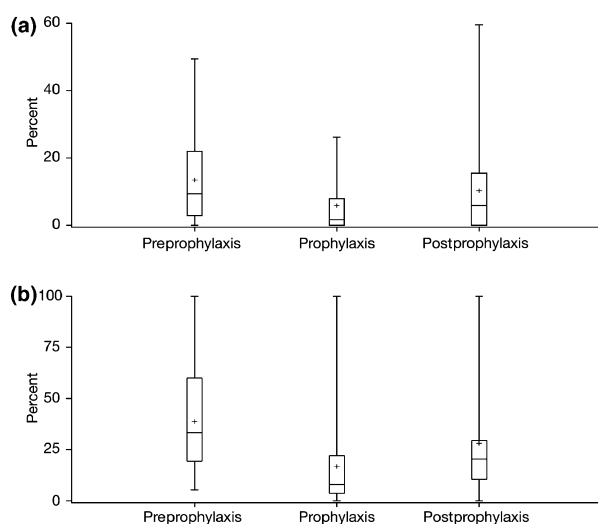


Fig. 1. Percentage of days in hospital (a) and days absent from school or work (b) before, during and after prophylaxis with recombinant activated factor VII.

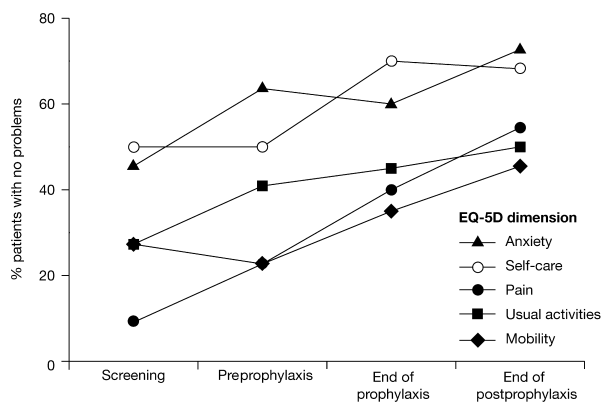


Fig. 2. Percentage of patients with no problems for each of the EQ-5D dimensions at screening, preprophylaxis, at the end of recombinant activated factor VII prophylaxis and at the end of the postprophylaxis period.

moderate or serious pain/discomfort compared with results for the preprophylaxis period, and 13.6% ($n = 3$) of patients reported no pain or discomfort. There was no shift in pain/discomfort experienced by 45% ($n = 9$) and 36.4% ($n = 8$) of patients with moderate or serious pain by the end of the prophylaxis and postprophylaxis periods respectively. A smaller number of patients reported an increase in pain over these periods (15% and 9.1%).

Patient mobility also tended to improve over the course of the trial (Fig. 2). During the preprophylaxis period, 22.7% of patients had NP walking (Fig. 2), 68.2% of patients had some problems walking and 9.1% were confined to bed. At the end of the prophylaxis and the postprophylaxis periods, mobility increased in 15% (3/20) and 27.3% (6/22) of patients, respectively, and 20.0% ($n = 4$) and 18.2% ($n = 4$) continued to have NPs walking during rFVIIa prophylaxis and postprophylaxis. Only one patient reported reduced mobility after the prophylaxis and postprophylaxis periods (5% and 4.5% respectively).

Most patients reported no change in the self-care, usual activity and anxiety/depression dimensions (prophylaxis: 80%, 85%, 65%; postprophylaxis: 81.8%, 72.7%, 68.2%) compared with the preprophylaxis period. Approximately half the patients had NPs with self-care (50%) and anxiety/depression (55%) by the end of rFVIIa prophylaxis vs. preprophylaxis values. Similarly, 50% of patients had NPs washing or dressing themselves and 59.1% of patients remained not anxious or depressed throughout the trial (end of postprophylaxis vs. preprophy-

laxis period). Improvements in these dimensions were reported in 18.2% and 18.1% of patients by study end, whereas no patient reported decreased self-care and only 9% of patients had worse anxiety/depression. There was a perceived improvement in activity in 15% of patients following rFVIIa prophylaxis, 30% had NP performing usual activities, and no change or a decrease in this dimension for 35% and 20% of patients respectively. Similarly, 22.7% of patients reported benefits in performing usual activities in the postprophylaxis vs. the preprophylaxis period, 36.4% had NPs, and 31.8% and 9% experienced no change or a decline in usual activities.

Ratings were inconsistent for one patient on the VAS score and two patients on the utility score (derived from inconsistencies in EQ-5D), and were thus considered outliers from the overall population. A non-parametric analysis was therefore used to reduce the influence of these values. Median VAS scores tended to increase throughout the course of the study (Table 2a), with absolute changes in VAS score between visits ranging from -60 to 60 (Table 2b). Median VAS increased significantly ($P = 0.048$) from preprophylaxis to the end of the postprophylaxis period (Table 2a, b).

Median TTO scores were 0.62, 0.73 and 0.76 at preprophylaxis, and at the end of prophylaxis and postprophylaxis respectively (Table 3a). The median difference of 0.10 (range -0.34 to 0.66) from preprophylaxis to the end of postprophylaxis was close to a significant change ($P = 0.054$) (Table 3a, b). The median TTO score increased by 0.06 during

Table 2. Summary of EQ-5D VAS score at screening, preprophylaxis, at the end of recombinant activated factor VII prophylaxis and at the end of the postprophylaxis period (a) and change in EQ-5D VAS score across visits (b).

	Screening	Preprophylaxis	End of prophylaxis	End of postprophylaxis	QALY
a: EQ-5D VAS score					
<i>n</i>	21	22	20	22	20
Mean	59.48	64.59	67.95	71.59	0.68
SD	15.32	20.06	21.43	20.36	0.18
Median	60.00	66.00	68.00	73.00	0.68
Range	30.00–80.00	29.00–100.00	30.00–100.00	40.00–100.00	0.40–1.00
Median diff*			4.00	6.50	
<i>P</i> -value*			0.257	0.048	
b: Absolute change in EQ-5D VAS score across visits†					
	End of prophylaxis		End of postprophylaxis		
	Difference from preprophylaxis		Difference from preprophylaxis		Difference from end of prophylaxis
<i>n</i>	20		22		20
Mean (SD)	3.65 (21.84)		7.00 (16.25)		3.80 (16.23)
Median (range)	4.00 (-60.00 to 37.00)		6.50 (-25.00 to 35.00)		0.00 (10.00–60.00)

n = number of patients.

*Median difference associated with Wilcoxon rank sum test with preprophylaxis visit as baseline and corresponding *P*-value.

†Data not available for two patients at the visit at the end of the prophylaxis period.

Table 3. Summary of EQ-5D TTO score at screening, preprophylaxis, at the end of recombinant activated factor VII prophylaxis and at the end of the postprophylaxis period (a) and change in EQ-5D TTO score across visits (b).

	Screening	Preprophylaxis	End of prophylaxis	End of postprophylaxis	QALY
a: EQ-5D TTO score					
<i>n</i>	22	22	20	22	20
Mean	0.54	0.56	0.61	0.69	0.62
SD	0.30	0.33	0.33	0.35	0.31
Median	0.62	0.62	0.73	0.76	0.73
Range	-0.16 to 1.00	-0.06 to 1.00	-0.06 to 1.00	-0.18 to 1.00	-0.06 to 0.95
Median diff [*]			0.06	0.10	
<i>P</i> -value [*]			0.456	0.054	
		End of prophylaxis	End of postprophylaxis		
		Difference from preprophylaxis	Difference from preprophylaxis	Difference from end of prophylaxis	
b: Absolute change in EQ-5D TTO score across visits [†]					
<i>n</i>		20	22	20	
Mean (SD)		0.03 (0.30)	0.13 (0.26)	0.09 (0.21)	
Median (range)		0.06 (-0.82 to 0.69)	0.10 (-0.34 to 0.66)	0.00 (0.17-0.82)	

n = number of patients.

^{*}Median difference associated with Wilcoxon rank sum test with preprophylaxis visit as baseline and corresponding *P*-value.

[†]Data not available for two patients at the visit at the end of the prophylaxis period.

rFVIIa prophylaxis compared with the preprophylaxis period, ranging from -0.82 to 0.69.

For the VAS score, effect sizes of 0.18 were found for the change from preprophylaxis to the end of prophylaxis and for the change from the end of prophylaxis to the end of postprophylaxis. An effect size of 0.34 was observed for change from baseline to the end of postprophylaxis. Effect sizes of 0.09 were found for the changes in TTO score from preprophylaxis to after prophylaxis, 0.39 for baseline to the end of postprophylaxis and 0.27 for after prophylaxis to the end of postprophylaxis. Median (range) QALYs were 0.68 (0.40-1.00) and 0.73 (-0.06-0.95) for VAS and TTO scores respectively (Table 2a and 3a).

Improvements in some HRQoL measures were observed between the screening and preprophylaxis (randomization) visits (Table 2a; Fig. 2), suggesting an effect of patient involvement in the trial on the HRQoL assessment (e.g. due to increased attention from clinicians). These findings support the use of the preprophylaxis visit as a baseline for comparing the effects of rFVIIa prophylaxis and postprophylaxis.

Correlation between bleeding and EQ-5D assessments

The mean number of bleeding episodes per month was negatively correlated with the mean VAS score (correlation coefficient = -0.46, *P* = 0.029; Fig. 3). No such correlation was seen for the number of bleeds vs. TTO score (correlation coefficient = -0.17, *P* = 0.446).

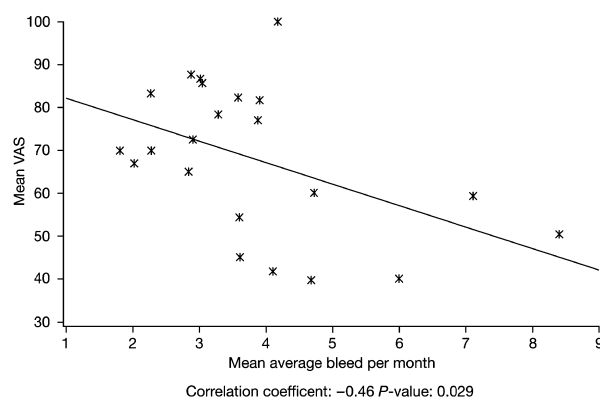


Fig. 3. Correlation between the mean number of bleeds per month and the mean EQ-5D VAS score during the preprophylaxis, prophylaxis and postprophylaxis periods.

Discussion

Secondary prophylaxis with rFVIIa significantly reduced the frequency of bleeding episodes compared with conventional on-demand therapy in inhibitor patients who bled frequently and overall had significant joint disease at the start of the trial. This effect persisted during the subsequent 3-month postprophylaxis period. The present analysis of this trial population extended these findings to suggest that the decrease in bleeding with 3 months of rFVIIa prophylaxis may also be translated into improvements in patients' HRQoL, particularly for pain and mobility problems, although these were not statistically significant.

Patients receiving rFVIIa prophylaxis for 3 months spent significantly less time in hospital and were less absent from school or work compared with conventional on-demand therapy during the preprophylaxis period. There was a non-significant trend for improvements in rates of hospitalization and absenteeism, with the effect of rFVIIa prophylaxis being maintained during the postprophylaxis period. Thus, the pattern of changes in these HRQoL measures appears similar to the significant differences observed for bleeding frequency among the three trial periods.

Reductions in time spent in hospital and absence from school or work with rFVIIa prophylaxis have also been reported in a number of case studies. Thus, our results are in accord with a recent retrospective survey of 13 adult and paediatric severe haemophilia patients with inhibitors, in which subjective HRQoL was improved, much improved or significantly improved with rFVIIa prophylaxis [17]. Additional case reports have demonstrated marked improvements in mobility, increased freedom from using a wheelchair, fewer days off work, or decreased time spent in hospital during rFVIIa [14–16] or aPCC [18] prophylaxis. More recently, a case study of a child with haemophilia and inhibitors reported a significant reduction in hospital administrations and significantly improved HRQoL with rFVIIa prophylaxis [30].

In addition to the improvements in the above pharmaco-economic outcomes, results from the EQ-5D questionnaire revealed a tendency for patients to perceive fewer pain and mobility problems with rFVIIa prophylaxis than when treatment was administered on demand, although these were not statistically significant. Approximately half of the patients (41%) perceived less pain and 27% of patients perceived an improvement in mobility after the postprophylaxis period compared with initial preprophylaxis. Corresponding values for the prophylaxis vs. preprophylaxis periods were 35% and 15%. There was a little change in the self-care, anxiety/depression or usual activities dimensions over the study. However, most patients in the study did not experience problems in these areas at the start of the study, so it was not possible to detect improvements. In addition, it is possible that the duration of treatment (3 months) may have been too short for significant improvements to have occurred.

Comparison of VAS scores demonstrated significantly better HRQoL after postprophylaxis with rFVIIa than in the preprophylaxis period (increase of 6.50; $P = 0.048$). This finding is consistent with the improvements seen in each of the EQ-5D-dimensions, in particular, pain and mobility. A smaller, non-significant difference of four in the VAS score

was observed following rFVIIa prophylaxis vs. the initial period of on-demand therapy.

Similar to the results of our study, approximately two thirds of patients reported some or MP with mobility or pain according to the EQ-5D profile in a study of haemophilia A patients with inhibitors and a low bleeding frequency (0.60 episodes per month) [8]. In a further analysis, 72% and 66% of moderate or severe haemophilia patients with inhibitors perceived moderate pain or problems in walking respectively [5]. In our study, 68.2% of patients reported moderate pain or mobility problems during the preprophylaxis period (63.6% and 77.3% respectively, at screening). In general, more problems appear to be perceived in relation to the physical domains in patients with haemophilia and inhibitors. Median EQ-VAS scores in these studies were similar at baseline [66 (range 30–95) [5,8] and 66 (29–100)]. When the EQ-5D profile was converted into a TTO score in the current study, there was a trend towards better HRQoL after the postprophylaxis period vs. the preprophylaxis period, but this was not statistically significant ($P = 0.054$). Median TTO scores were comparable with those reported previously for patients with moderate or severe haemophilia A and high-responding inhibitors (0.69), according to UK conversion values (–0.545 to 1.00) [8], indicating that serious health problems are perceived by some inhibitor patients. The VAS and TTO scores in these patients with inhibitors are also comparable with those reported for severe haemophilia patients without inhibitors who had not received primary prophylaxis [median (range): 70 (20–98) and 0.66 (–0.48 to 1.00)] [29]. It has previously been questioned whether UK population weights should be applied to an international population. However, weights are not available for all countries in our study, and no international weights currently exist. Further, a recent study has shown that although it is preferable to use specific population weights for each country, applying only one population weight is unlikely to lead to very different results [31].

Effect sizes between trial periods were small to moderate for the VAS (0.18–0.34) and TTO (0.09–0.39) scores, according to the generally accepted benchmarks (0.20 and 0.50 for small and moderate effect sizes respectively) [24]. Nevertheless, differences between trial periods were above 0.03, the smallest difference on the EQ-5D index that represents a transition between levels within a domain [32]. The effect size was highest from the preprophylaxis visit to after the postprophylaxis period (0.34 for VAS and 0.39 for TTO scores). It should be noted that patients only received rFVIIa prophylaxis

for 3 months in this study; had this been extended, the benefits of treatment might have been greater.

The results for HRQoL were consistently better at the end of the postprophylaxis period than at the end of the prophylaxis period, whereas the average number of bleeds was higher during the postprophylaxis period than with rFVIIa prophylaxis (median increase of 11.2%). This could be attributed to a 'time lag' between treatment and effect; this delayed effect may be more pronounced in patients with chronic disease who are severely disabled. There was also a significant negative correlation between the mean number of bleeding episodes per month and the mean VAS score, which could be explained by changes in the rate of hospitalization. The trend for the improvements in HRQoL to persist into the postprophylaxis period suggests that secondary prophylaxis with rFVIIa may have lasting positive effects for patients with inhibitors. It is possible that this may result from an intermediate benefit of prophylactic therapy in reducing haemarthroses after the period of prophylaxis had ended, which would be consistent with data for secondary prophylaxis in non-inhibitor patients [9,33]. For example, Manco-Johnson *et al.* have recently proposed that prophylaxis may prevent chronic microhaemorrhage into the joints or subchondral bone in young haemophilia patients, which could otherwise result in subclinical deterioration of joints [33].

The improved patient TTO score and VAS with rFVIIa prophylaxis resulted in a median gain of 0.10 and 6.5 respectively (Tables 3a and 2a). The preprophylaxis median TTO score of 0.62 and baseline median VAS of 66 are slightly lower but comparable with those reported by Miners *et al.* [29] of 0.66 and 70, respectively, based on 66 severe haemophilia patients not on prophylaxis. Mild/moderate haemophilia patients scored a median TTO of 0.85 and a median VAS of 80 (based on 100 patients), which are higher than the median TTO score of 0.76 and median VAS of 73 reported at the end of the postprophylaxis period (Table 3a and 2a). Confirmatory studies are required to confirm whether the treatment is cost-effective, as suggested by other studies. For primary prophylaxis in non-inhibitor patients, the use of different methodology (theoretical Markov modelling of lifetime costs of treatment) has suggested that prophylaxis would result in an additional 14.8 QALYs compared with on-demand treatment (mean QALYs of 41.1 and 55.9 for on-demand and primary prophylaxis treated patient, respectively), and may therefore offer important clinical benefits despite its high cost [34].

The results of this prospective trial, the first to evaluate rFVIIa prophylaxis in haemophilia patients with inhibitors and frequent bleeds, have shown positive and promising findings for HRQoL outcomes. However, the analysis is based on a few patients and the questionnaires used were not specific to haemophilia patients and were only validated in adults. Future studies need to be performed with the newly developed and validated HRQoL questionnaires now available for patients with haemophilia. It should also be noted that although patients were randomized, double-blind, to rFVIIa dose, this was not the case for comparisons between trial periods.

Conclusion

The results of this prospective trial suggest that secondary prophylaxis with rFVIIa may improve a variety of important measures of patient HRQoL (VAS and EQ-5D) in frequently bleeding inhibitor patients compared with conventional on-demand therapy. No clear difference between a low dose and high dose of rFVIIa was observed.

Together with the clinically relevant reductions in the number of bleeds and absence of safety concerns, these HRQoL findings suggest that secondary rFVIIa prophylaxis may provide an alternative treatment modality to conventional treatment regimens for inhibitor patients with frequent bleeds. Improved HRQoL with secondary rFVIIa prophylaxis may thus provide inhibitor patients with an opportunity for improved life quality.

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Appendix

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