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ORIGINAL ARTICLE *Clinical haemophilia*

Modelling lifelong effects of different prophylactic treatment strategies for severe haemophilia A

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Background: Lifelong prophylactic replacement therapy with clotting factor concentrates is recommended for severe haemophilia. The prophylactic dose determines both clinical outcome and treatment cost. In the absence of clinical studies, computer simulation was used to explore lifelong effects and clotting factor consumption for various prophylactic dose levels, and optimize strategies for switching between prophylactic and on-demand treatment. **Design and Methods:** Individual patients' lifetime joint bleeds, radiological arthropathy (Pettersson score, 0–78) and consumption were simulated for each treatment strategy. Treatment effectiveness (expressed as % of patients maintaining a lifetime Pettersson score ≤14) and clotting factor consumption were modelled for lifelong prophylaxis at dose levels 1000–4500 IU kg^{-1} $year^{-1}$, for on-demand treatment and for switching strategies. Treatment efficiency (consumption per unit of effectiveness) was used to compare strategies. **Results:** Compared to lifelong on-demand treatment, lifelong prophylaxis at 1000 IU kg^{-1} $year^{-1}$ increased effectiveness from 21 to 36%, at an additional consumption of 0.9×10^6 IU kg^{-1}. For lifelong prophylaxis, each additional 1000 IU kg^{-1} $year^{-1}$ resulted in a proportional increase in consumption by $\pm 5 \times 10^6$ IU kg^{-1} but a less than proportional reduction in arthropathy by ±50%; consequently, increasing consumption progressively diminished treatment efficiency. Switching strategies slightly reduce effectiveness and consumption. Optimum switching criteria were similar across prophylactic dose levels. **Conclusion:** According to the simulation model, low-dose prophylaxis (1000 IU kg^{-1} $year^{-1}$) improved outcome at a limited increase in consumption compared to on-demand treatment. Increasing prophylactic dose further improved health outcomes, but at decreasing efficiency. Optimal prophylactic dose should therefore be selected balancing acceptable health impact and available budget.

Keywords: arthropathy, clotting factor consumption, computer simulation model, dose, episodic treatment, haemarthrosis

Introduction

Severe haemophilia A is a rare disease, characterized by absence of clotting factor VIII (FVIII), requiring life-long expensive replacement therapy with clotting factor concentrates. In these patients, repeated joint bleeding eventually leads to crippling and painful arthropathy, usually occurring only in adulthood [1]. Traditional treatment was on demand, i.e. in case of bleeding, only. Prophylactic replacement therapy, i.e. regular infusions of FVIII in the absence of bleeding, was introduced in the 1960s to prevent bleeding and subsequent arthropathy [2]. Different prophylactic regimens have been used since then; while the frequency of prophylactic infusions used in these regimens is similar (usually 3–3.5× per week), dose and duration of prophylaxis vary considerably. It is well established that the cost of clotting factor concentrates accounts for >90% of the cost of haemophilia treatment [3,4]. Therefore, it is important to establish the relationship between dose and response, especially in prophylaxis [5].

Concerning prophylactic dose, most countries have followed the successful Swedish prophylactic regimen, in spite of its high consumption and costs. This regimen originally aimed at maintaining minimum trough levels of clotting factor activity using FVIII doses of

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25–40 IU kg^{-1} 3× per week or every other day for haemophilia A [2,6]. In the Netherlands however, prophylaxis was aimed at preventing spontaneous joint bleeds using 10–15 IU kg^{-1} per infusion only, while intervals were the same [7]. Recently, a comparison of these regimens with 24 years of follow up showed that the high dose regimen resulted in a small improvement of outcome at a 66% increased annual cost (from mean 180×10^3 to 298×10^3 USD per year) [8].

Based on the observation that some patients may be able to discontinue prophylaxis in adulthood [9,10], switching to on-demand treatment after covering the period of growth with prophylaxis may be used as a strategy to deliver less intensive treatment to patients with milder bleeding patterns. In order to avoid frequent bleeding, criteria for safely discontinuing prophylaxis should be established.

Ideally, a randomized study spanning several decades, which includes different dosing regimens as well as treatment arms with a switch to on-demand treatment in early adulthood, should be performed to compare the effects of different regimens. However, the long-term follow-up required [7,11]; and the low number of patients available render this design infeasible for the comparison of prophylactic strategies [12]. Studies modelling patient treatment and outcome are a method used to circumvent this problem [13–16]. Our group designed a micro simulation model based on data from existing cohorts [17]. The model allows comparing on-demand treatment, intermediate-dose prophylaxis, and various strategies switching between these two for treatment of severe haemophilia A. It was updated by adding information generated by expert judgment elicitation [18].

This paper explores the effects of different prophylactic dose levels for severe haemophilia A compared to lifelong on-demand treatment, as well as the optimum criteria for switching between prophylactic and on-demand treatment.

Methods

Model outline

Details on the structure and operation of the previous model for simulating haemophilia treatment strategies were described elsewhere [17]. In short, based on distributions of actual data, the model assigns a random age of first joint bleed, adult weight, life expectancy and baseline bleeding frequency to each patient entering the cohort. For on-demand treatment, the annual number of joint bleeds is determined by the patient's bleeding tendency only, for prophylactic treatment strategies, it is determined by both bleeding tendency and the effectiveness of treatment. The model generates cohorts of 2000 individual patients with different patient characteristics. In each simulation, lifelong treatment according to a particular treatment regimen is applied to this cohort and the lifetime number of joint bleeds, clotting factor consumption and joint damage (radiological Petterson score [19]) is determined for each patient. This study used a second version of this simulation model, which was extended with estimates of the bleeding frequency for on-demand treatment, the prophylactic dose required to suppress different bleeding tendencies, the dose required for treatment of minor bleeds, and the relative life expectancy of haemophilia patients. These estimates were generated by a formal expert elicitation procedure including 19 international haemophilia experts [18]. The study was approved by the Ethical Committee of the University Medical Center Utrecht.

To facilitate comparison of different prophylactic regimens and different switching strategies, treatment efficiency (defined as clotting factor consumption per unit of effectiveness) was calculated for each strategy. Treatment effectiveness was defined as the proportion of patients with a total Pettersson score of ≤14 points at the end of life. This threshold was subjectively chosen as half the threshold of 28 points, associated with decreased physical functioning and increased disability in patients aged 40.6 years (SD 7.5) [20].

Exploration of the effects of prophylactic dose

For lifelong prophylaxis, the model was set to start with prophylaxis after the first-joint bleed and continue at constant dosing levels between 1000 and 4500 IU kg^{-1} $year^{-1}$ at increments of 500 IU kg^{-1} $year^{-1}$. Lifelong on-demand treatment was modelled to provide a reference group.

Exploration of different bleeding criteria for switching strategies

For the evaluation of switching strategies, the model was set to start prophylaxis after the first joint bleed and continue prophylaxis until the age of 18 years. From this age onwards, prophylaxis continued, but if the patient experienced a maximum of one joint bleed in three consecutive years, treatment was changed to a 'switching' treatment strategy. This strategy allows for repeated switching between prophylaxis and on-demand treatment depending on observed joint bleeding. The maximum number of switches from prophylaxis to on-demand treatment was eight per patient.

Various switching strategies were defined according to the number of joint bleeds accepted over a certain period: after discontinuing prophylaxis, a patient would remain on on-demand treatment unless he showed more than a particular number (B1) joint bleeds per year in one, B2 joint bleeds per year in

two, or B3 joint bleeds per year in three consecutive years. For each prophylactic dose level, the 'optimum' switching strategy was identified. This was the strategy that showed the highest efficiency (lowest consumption per unit of effectiveness) for achieving the targeted 'effectiveness' of a lifetime Pettersson score of maximum 14 points. In addition to the optimum switching criteria and patient outcome, the model provided information on the proportion of patients ever switching from prophylaxis to on-demand treatment.

Results

The effects of different prophylactic dose levels

The effect of lifelong on-demand treatment and lifelong prophylaxis at various dose-levels on Pettersson scores according to age are shown in Fig. 1. It clearly shows that compared to lifelong on-demand treatment, prophylaxis prevents arthropathy in a dose-dependent manner. Moreover, it suggests that the efficiency decreases with increasing prophylactic dose levels. Table 1 provides additional data on the cumulative number of joint bleeds, Pettersson scores and clotting factor consumption at different ages (results for additional dose levels are presented as Appendix S1). Compared to on-demand treatment, prophylaxis at 1000 IU kg^{-1} $year^{-1}$ resulted in an approximately 50% reduction in joint bleeds at the end of life, with a 71% increase in effectiveness (from 21 to 36%) at an increased clotting factor consumption of only 0.9×10^6 IU (from 3.9 to 4.8 $\times$ 10^6 IU). When comparing the different dose levels of prophylaxis, the increase in consumption was proportional: for each 1000 IU kg^{-1} $year^{-1}$ increase in prophylactic dose, lifetime consumption increased by ± 5 million IU kg^{-1}, while bleeding and Pettersson scores showed a less than proportional reduction in approximately 50%. Consequently, increasing prophylactic dose levels progressively diminishes treatment efficiency.

Optimum switching strategy

The optimum switching criteria were determined for each prophylactic dose level based on the criteria of highest efficiency (i.e. lowest consumption per % of patients with a life-time Pettersson score $\leq$14 points). Switching strategies were defined as the number of joint bleeds in any year (B1), and in two (B2) or three (B3) consecutive years, respectively, that would trigger the re-institution of prophylaxis in patients who had switched to on-demand treatment in adulthood. No distinction between spontaneous or trauma-related bleeding was made. Table 2 shows the optimum switching criteria and their effects on lifetime clotting factor consumption and effectiveness. Eventual switching criteria were very similar for different dose levels (Table 2) and differences in consumption and effectiveness of different criteria were very small (Appendix S1). If one would apply the most stringent criteria of 8-6-5; i.e. eight joint bleeds in any year, $\geq$6 per year in two consecutive years, or $\geq$5 per year in three consecutive years, this would result in only very limited changes in consumption and effectiveness as presented in Table 2. The proportion of patients eventually remaining on on-demand treatment remained quite stable between 23 and 32%.

Figure 2a shows lifetime clotting factor consumption, and Fig. 2b shows treatment effectiveness according to different treatment strategies, including multiple switching. When considering lifetime prophylaxis regimens at increasing dose levels, these figures again show that consumption increases progressively, but that the incremental effectiveness diminishes. When comparing the outcome of switching strategies with lifelong

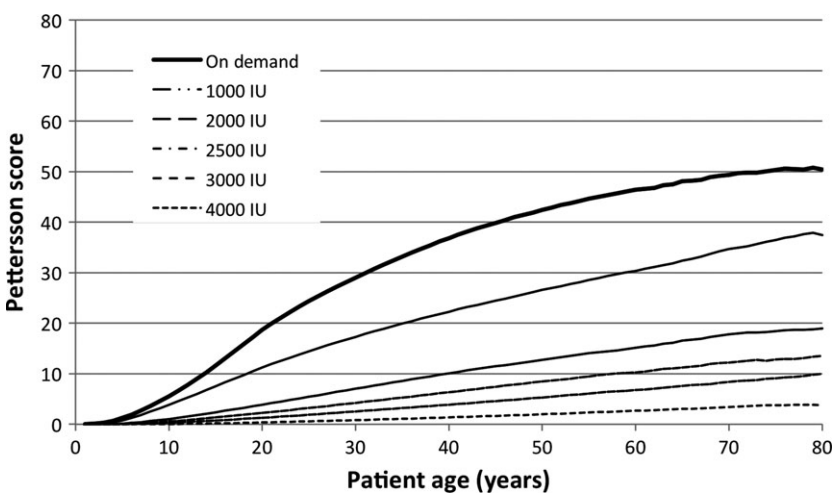

Fig. 1. Mean Pettersson scores according to age and treatment regimen (prophylaxis at various annual dose levels and lifelong on-demand treatment).

Table 1. Results of on-demand treatment and full prophylactic strategies according to age and different annual prophylactic doses.

Treatment			Full prophylaxis				
Prophylactic dose, IU kg^{-1} $year^{-1}$	Age	On demand	1000 IU	2000 IU	2500 IU	3000 IU	4000 IU
Cumulative nr of Joint Bleeds	20	287 (12–1095)	184 (7–942)	80 (4–437)	54 (4–324)	38 (4–235)	20 (3–114)
Pettersson score		19 (0–78)	11 (0–69)	4 (0–30)	2 (0–22)	1 (0–15)	0 (0–5)
Pettersson score ≤14		56%	77%	92%	95%	98%	100%
Cumulative Clotting factor use (IU × 10^6)		0.50 (0.02–2.0)	0.79 (0.74–0.81)	1.6 (1.5–1.6)	2.0 (1.9–2.0)	2.4 (2.2–2.4)	3.2 (3.0–3.2)
Cumulative nr of Joint Bleeds	40	698 (17–3099)	388 (17–1974)	169 (11–923)	115 (10–687)	80 (10–507)	43 (9–232)
Pettersson score		37 (0–78)	22 (0–78)	10 (0–69)	6 (0–51)	4 (0–35)	1 (0–15)
Pettersson score ≤14		33%	53%	79%	87%	91%	98%
Cumulative Clotting factor use (IU × 10^6)		1.7 (0.03–7.9)	2.2 (2.2–2.3)	4.5 (4.4–4.5)	5.6 (5.5–5.6)	6.7 (6.6–6.8)	8.9 (8.8–9.0)
Cumulative nr of Joint Bleeds	60	1115 (20–5158)	597 (26–3017)	257 (19–1417)	175 (17–1064)	124 (16–766)	67 (15–362)
Pettersson score		46 (0–78)	30 (0–78)	15 (0–78)	10 (0–78)	7 (0–57)	3 (0–25)
Pettersson score ≤14		24%	42%	67%	79%	86%	94%
Cumulative Clotting factor use (IU × 10^6)		2.9 (0.04–14)	3.7 (3.6–3.7)	7.4 (7.3–7.4)	9.2 (9.1–9.2)	11 (11–11)	15 (15–15)
Cumulative nr of Joint Bleeds	Life-time	1465 (22–6988)	761 (36–3977)	326 (23–1857)	223 (20–1310)	158 (20–982)	85 (18–482)
Pettersson score		50 (0–78)	35 (0–78)	19 (0–78)	13 (0–78)	9 (0–74)	4 (0–34)
Pettersson score ≤14		21%	36%	62%	74%	82%	92%
Cumulative Clotting factor use (IU × 10^6)		3.9 (0.04–19)	4.8 (3.1–6.1)	9.6 (5.9–12)	12 (7.6–16)	14 (9.2–19)	19 (12–25)

Data are mean values (95% confidence interval).

prophylaxis, Table 2 and Fig. 2a show that switching results in a reduction in consumption ranging from 17% in the lowest, to 32% in the highest prophylactic dose. Concomitantly, Table 2 and Fig. 2b show that switching strategies result in similar joint damage for dose levels up to 2000 IU kg^{-1} $year^{-1}$, but a progressive reduction in outcome for higher prophylactic dose levels. These two trends are reflected in the column with the efficiency data.

Discussion

Using a computer model simulating lifetime treatment of individual patients, the study aimed to explore the effects of lifelong prophylaxis and switching strategies at different dose levels. Compared to lifelong on-demand treatment, lifetime prophylaxis at 1000 IU kg^{-1} $year^{-1}$ resulted in significantly improved outcome at a limited increase in clotting factor consumption. Increasing prophylactic dose resulted in a proportional increase in lifetime clotting factor consumption ($\pm 5 \times 10^6$ IU kg^{-1}), however with a diminishing incremental effectiveness. The optimum criteria for switching between prophylactic and on-demand treatment were similar across prophylactic dose levels. For the switching strategies, there was no increase in effectiveness beyond 3000 IU kg^{-1} $year^{-1}$, but consumption was reduced as compared to lifelong prophylaxis.

The present model allows exploration of the lifetime impact of various treatment strategies on outcome and consumption. Outcome of prophylaxis was superior to lifelong on-demand treatment, but the lowest dose regimen had a limited effectiveness of 36%. As higher dosed regimens had both improved effectiveness and increased consumption (and thus cost), the choice for the prophylactic dose will depend on clinical considerations and on the availability and cost of clotting factor concentrates.

Model design

The validity of any computer model depends heavily on its inputs and assumptions. The first version of the model was based on actual patient data only. As not all data were available from clinical sources, a formal expert elicitation method was used to provide estimates on life expectancy, treatment of minor bleeds, bleeding during on-demand treatment and the dose-effect of prophylaxis. Especially the latter two parameters have a large impact on the estimates of lifelong effects and consumption of various prophylactic dose levels. The expert estimates for bleeding during on-demand treatment in adults used in the model, ranging from 9 to 16 per year (95% confidence interval 1–66), are similar to the 16.7 joint bleeds per year reported in the POTTER study [21] and slightly lower than the 20.1 reported in the SPINART study [22]. Both studies included patients with a mean age of 24 and 30 years respectively.

To obtain a clinically relevant outcome parameter, the threshold of 'effectiveness' used in the comparison of regimens was subjectively chosen as half the threshold of 28 points, associated with decreased physical functioning and increased disability in patients aged 40.6 years [20]. This threshold is actually quite close

Table 2. Optimum switching strategies, effects, and consumption of lifetime prophylaxis and switching strategies according to prophylactic dose.

			Effectiveness		Consumption		Efficiency	
			Proportion of patients with Pettersson score ≤14 points at the end of life		Lifetime clotting factor consumption IU × 10^6 kg (mean)		Consumption per % effectiveness: IU × 10^6/kg/% point	
Treatment Prophylactic dose IU kg^{-1} $year^{-1}$	Optimum switching strategy (B1, B2, B3)*	% staying on on-demand	Lifetime prophylaxis, %	Switching strategy, %	Lifetime prophylaxis	Switching strategy	Lifetime prophylaxis	Switching strategy
1000	10, 7, 4	23	36	36	4.8	4.0	0.134	0.110
1500	10, 7, 4	28	49	49	7.3	5.7	0.149	0.116
2000	8, 6, 5	29	62	60	9.6	7.3	0.155	0.122
2500	8, 6, 5	33	74	69	12.1	8.9	0.163	0.129
3000	9, 7, 6	31	82	72	14.5	10.1	0.177	0.140
3500	10, 7, 4	32	88	77	16.9	11.9	0.192	0.155
4000	9, 7, 5	31	92	77	19.4	13.3	0.210	0.172
4500	9, 7, 5	31	95	77	21.8	14.9	0.229	0.194

*Switching strategy: patients start prophylaxis after their first joint bleed until age 18. From this age onwards, prophylaxis continued, but if the patient experienced ≤1 joint bleed in three consecutive years, he may switch to on-demand treatment and would remain on on-demand treatment unless he showed more than B1 joint bleeds per year in one, B2 joint bleeds per year in two or B3 joint bleeds per year in three consecutive years.

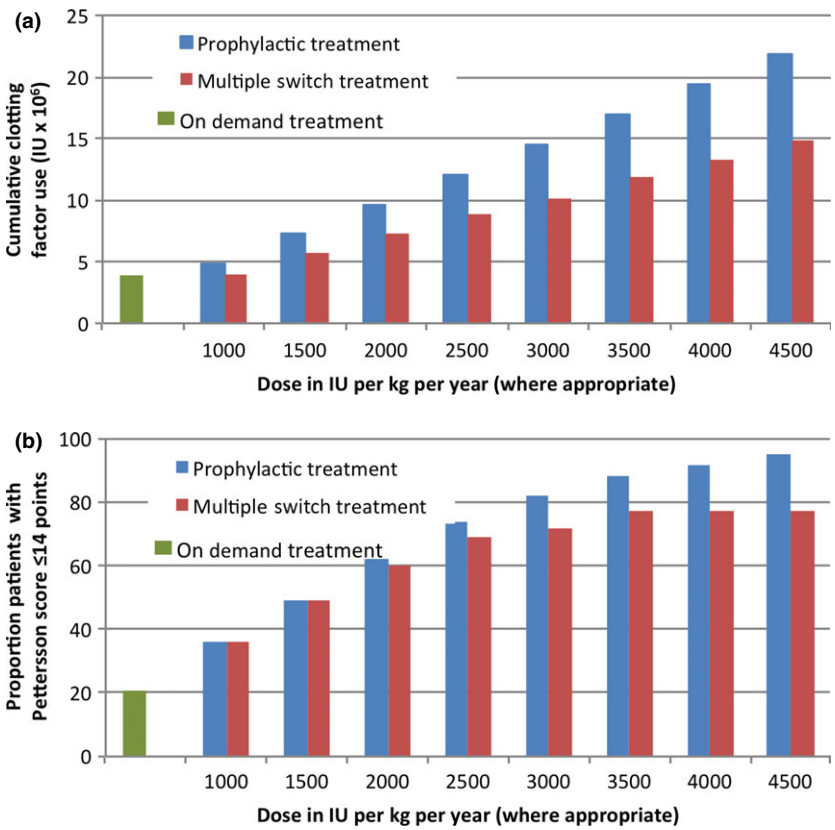

Fig. 2. (a) Lifetime clotting factor consumption according to different prophylactic dose levels including multiple switching strategies. (b) Percentage of patients with a Pettersson score ≤14 points at the end of life according to different prophylactic dose levels including multiple switching strategies.

to the threshold considered associated with loss of function by the experts (median Pettersson 5 points per joint, interquartile range 3–6.5) [18], as most haemophilia patients have 2–3 joints affected by arthropathy [8]. However, in addition to median Pettersson scores at different analyses with different thresholds could easily be performed, as the model generates lifetime Pettersson scores according to treatment strategy for each patient.

Rather than a full economic evaluation, the current model is intended for evaluating the impact of prophylactic dose levels and various switching criteria. In this model, costs are only included as clotting factor consumption, but these represent >90% of direct medical costs [3,4]. Therefore, it may be used to evaluate some economic aspects of treatment. For example, the effect of different price levels of clotting factor concentrates can be directly appreciated from the model output.

For extended half-life concentrates, however, both prophylactic dose and the relation between dose and bleeding suppression will be affected, and the model needs to be updated before it can be applied.

Comparison with published data

Several model estimates were in accordance with results from the Expert Judgement Elicitation process preceding the update of the current model. The proportion of patients eventually remaining on on-demand treatment was in accordance with their estimate of 30% (IQR 25–45%) [18]. So was the optimum switching strategy: for adults with intact joints treated on-demand, the experts considered up to six joint bleeds per year (IQR 3–9) acceptable. Based on the switching criteria of 8-6-5, the maximum accepted annual number of joint bleeds was well within these limits at seven in any year, five in two consecutive years, or four in three consecutive years.

Unfortunately, data on radiological outcome for different treatment strategies are still scant. In the POTTER study, Pettersson scores were available for only nine patients treated on demand [21], the SPINART study performed MRI evaluation only [22]. Comparisons with earlier reports including Pettersson scores [23,24] are hampered by inadequate access to treatment in older patients and the late onset of prophylaxis. The estimated mean Pettersson score at age 20 years for patients treated on demand (19 points) was in accordance with the mean Pettersson score of 18.8 points in 54 French patients with severe haemophilia A at the age of 23 years reported by Molho *et al.* [4].

Already in 2004, professor Srivastava wrote a review on treatment dose and response, suggesting that the association of joint outcome and treatment dose might not be proportional. The present model is the first to confirm this hypothesis. So far, several other groups have simulated life-long haemophilia treatment using computer models [13–17]. However, most of them used Markov modelling, and all were focused on economic evaluations, using cost per QALY as outcome parameters. None have included an analysis of the effects of treatment on joint status, but all reported that treatment costs are highly dependent on FVIII consumption and price. Interestingly, Colombo *et al.* [15] corroborated the finding of reduced treatment costs following a switching scenario between prophylactic and on-demand treatment in adulthood.

Implications for management and decision-making

The information on the effects of different prophylactic dose levels can be used when choosing prophylactic regimens, e.g. at the centre level. At the patient level, individualization of treatment dose will be necessary for some patients. This is currently not included in our model: each prophylactic regimen represents a fixed prophylactic dose only. Furthermore, it must be emphasized that this model reflects a setting of unlimited availability of clotting factor concentrates, the use of home-infusion, and prophylaxis started after the first joint bleed. This model cannot be used to study secondary prophylaxis, which is less effective in preventing arthropathy [25,26].

Regarding the switching between prophylaxis and on-demand treatment in adults, the potential clinical use of these findings are limited by the recent observation of increased arthropathy in patients who switched to on-demand treatment in adulthood. While reporting equally low bleeding rates as patient on prophylaxis, these patients showed an unexpected and significant increase in Pettersson scores after 10 years of on-demand treatment [27]. Therefore, arthropathy is likely underestimated for the multiple switch strategies and results should be interpreted with caution. Based on these new findings, switching between dose levels may be preferred over switching between prophylactic and on-demand treatment.

Regarding the choice of prophylactic dose levels, the model shows that compared to on-demand treatment, the lowest dose of 1000 IU kg^{-1} $year^{-1}$ (i.e. 2× per week 10 IU kg^{-1}) improves outcome at a limited increase in consumption. Moreover, both effectiveness and consumption continue to increase up to the level of 4500 IU kg^{-1} $year^{-1}$ (i.e. 3–3.5× per week 25 IU kg^{-1}). The information provided on long-term outcome and effectiveness of different prophylactic regimens is most valuable for clinical decision-making regarding prophylactic dose. The information on efficiency was only used to compare regimens whose clinical relevance cannot be assessed. Because efficiency progressively decreases with increasing dose, it cannot be used as the sole criterion to identify the optimum prophylactic regimen. Instead, clinical considerations regarding the target level of protection for patients should be combined with availability and the cost of clotting factor concentrates in the context of the budget available.

Future research

To validate the present model, its estimates should be compared to real-life data on joint outcome (Pettersson scores) in patients treated on demand, patients using high-dose prophylaxis and patients who discontinued prophylaxis. To check the threshold used for effectiveness, additional information on the association of arthropathy, health-related quality of life, and work force participation is needed [5]. Addition of the

utility values associated with different levels of arthropathy, inclusion of data on costs of concentrates, inhibitor development, orthopaedic surgery and work participation will enable the use of this model for full economic evaluations [28].

Conclusion

Using a computer modelling approach, lifetime outcome and consumption of various treatment strategies were compared. Compared to lifelong on-demand treatment, lifetime prophylaxis at 1000 IU kg^{-1} $year^{-1}$ resulted in significantly improved outcome at a limited increase in clotting factor consumption. Increasing prophylactic dose levels were associated with a proportional increase in lifetime consumption, but a less than proportional improvement of outcome. The present data provide information that may help choose prophylactic treatment regimens based on the target level of protection combined with availability and the cost of clotting factor concentrates.

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Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

References

1 Ahlberg A. Haemophilia in Sweden VII. Incidence, treatment and prophylaxis of arthropathy and other musculo-skeletal manifestations of haemophilia A and B. *Acta Orthop Scand* 1965; **77**(suppl): 5–99.
2 Nilsson IM, Hedner U, Ahlberg A. Haemophilia prophylaxis in Sweden. *Acta Paediatr Scand* 1976; **65**: 129–35.
3 Miners AH, Sabin CA, Tolley KH, Lee CA. Assessing the effectiveness and cost-effectiveness of prophylaxis against bleeding in patients with severe haemophilia and severe von Willebrand's disease. *J Intern Med* 1998; **244**: 515–22.
4 Molho P, Rolland N, Lebrun T *et al.* Epidemiological survey of the orthopaedic status of severe haemophilia A and B patients in France. *Haemophilia* 2000; **6**: 23–32.
5 Srivastava A. Dose and response in haemophilia–optimization of factor replacement therapy. *Br J Haematol* 2004; **127**: 12–25.
6 Berntorp E, Astermark J, Bjorkman S *et al.* Consensus perspectives on prophylactic therapy for haemophilia: summary statement. *Haemophilia* 2003; **9**(Suppl 1): 1–4.
7 Fischer K, van der Bom JG, Mauser-Bunschoten EP *et al.* Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy. *Haemophilia* 2001; **7**: 446–52.
8 Fischer K, Steen Carlsson K, Petrini P *et al.* Intermediate-dose versus high-dose prophylaxis for severe hemophilia: comparing outcome and costs since the 1970s. *Blood* 2013; **122**: 1129–36.
9 van Dijk K, Fischer K, van der Bom JG, Scheibel E, Ingerslev J, van den Berg HM. Can long-term prophylaxis for severe haemophilia be stopped in adulthood? Results from Denmark and the Netherlands. *Br J Haematol* 2005; **130**: 107–12.
10 Richards M, Altisent C, Batorova A *et al.* Should prophylaxis be used in adolescent and adult patients with severe haemophilia? An European survey of practice and outcome data. *Haemophilia* 2007; **13**: 473–9.
11 Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med* 1992; **232**: 25–32.
12 Fischer K, Grobbee DE, van den Berg HM. RCTs and observational studies to determine the effect of prophylaxis in severe haemophilia. *Haemophilia* 2007; **13**: 345–50.
13 Smith PS, Teutsch SM, Shaffer PA, Rolka H, Evatt B. Episodic versus prophylactic infusions for hemophilia A: a cost-effectiveness analysis. *J Pediatr* 1996; **129**: 424–31.
14 Miners A. Revisiting the cost-effectiveness of primary prophylaxis with clotting factor for the treatment of severe haemophilia A. *Haemophilia* 2009; **15**: 881–7.
15 Colombo GL, di Matteo S, Elisa Mancuso M, Santagostino E. Cost-utility analysis of prophylaxis versus treatment on demand in severe hemophilia A. *Clinicoecon Outcomes Res* 2011; **3**: 55–61.
16 Farrugia A, Cassar J, Kimber MC *et al.* Treatment for life for severe haemophilia A- A cost-utility model for prophylaxis vs. on-demand treatment. *Haemophilia* 2013; **19**: e228–38.
17 Fischer K, Pouw ME, Lewandowski D, Janssen MP, van den Berg HM, van Hout BA. A modeling approach to evaluate long-term outcome of prophylactic and on demand treatment strategies for severe hemophilia A. *Haematologica* 2011; **96**: 738–43.
18 Fischer K, Lewandowski D, Janssen MP. Estimating unknown parameters in haemophilia using expert judgement elicitation. *Haemophilia* 2013; **19**: e282–8.
19 Hamel J, Pohlmann H, Schramm W. Radiological evaluation of chronic hemophilic arthropathy by the Pettersson score: problems in correlation in adult patients. *Skeletal Radiol* 1988; **17**: 32–6.
20 Fischer K, Bom JG, Mauser-Bunschoten EP, Roosendaal G, Berg HM. Effects of haemophilic arthropathy on health-related quality of life and socio-economic parameters. *Haemophilia* 2005; **11**: 43–8.
21 Tagliaferri A, Feola G, Molinari AC *et al.* Benefits of prophylaxis versus on-demand treatment in adolescents and adults with severe haemophilia A: the POTTER study. *Thromb Haemost* 2015; **114**: 35–45.
22 Manco-Johnson MJ, Kempton CL, Reding MT *et al.* Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART). *J Thromb Haemost* 2013; **11**: 1119–27.
23 Aledort LM, Haschmeyer RH, Pettersson H. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. The Orthopaedic Outcome Study Group. *J Intern Med* 1994; **236**: 391–9.
24 Löfqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients–a long-term follow-up. *J Intern Med* 1997; **241**: 395–400.
25 Astermark J, Petrini P, Tengborn L, Schulman S, Ljung RCR, Berntorp E. Primary prophylaxis in severe haemophilia should be started at an early age but can be individualized. *Br J Haematol* 1999; **105**: 1109–13.
26 Fischer K, van der Bom JG, Mauser-Bunschoten EP *et al.* Effects of postponing prophylactic treatment on long-term outcome in patients with severe haemophilia. *Blood* 2002; **99**: 2337–41.

27 Nijdam A, Foppen W, de Kleijn P *et al.* Discontinuing early prophylaxis in severe haemophilia leads to deterioration of joint status despite low bleeding rates. *Thromb Haemost* 2016; **115**: 931–8.
28 Nicholson A, Berger K, Bohn R *et al.* Recommendations for reporting economic evaluations of haemophilia prophylaxis: a nominal groups consensus statement on behalf of the Economics Expert Working Group of The International Prophylaxis Study Group. *Haemophilia* 2008; **14**: 127–32.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Modelling lifelong treatment for severe haemophilia.