Treatment for Life for Severe Haemophilia A – A Cost-Utility Model

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Abstract

Introduction. Prophylaxis has been established as the treatment of choice in children with haemophilia and its continuation into the adult years has been shown to decrease morbidity throughout life. The cost of factor therapy has made the option questionable in cost-effectiveness studies.

Aim. The role of prophylaxis in pharmacokinetic dosage and tolerisation against inhibitor formation were used to model the cost-utility of prophylaxis versus on-demand (OD) therapy over a lifetime horizon in severe haemophilia A.

Methods. Commercial software (TreeAge™) was used to construct a Markov model with 80 cycles of one year each. The model was populated with variables for costs and effectiveness for haemophilia outcomes including joint and soft tissue bleeds, inhibitors and dosage. Key inputs into the model which differed from previous exercises included the use of pharmacokinetic dosage and effect of prophylaxis on the probability of developing inhibitors.The model was applied to a single provider national health system exemplified by the United Kingdom's National Health Service and a third party provider in the United States. The incremental cost effectiveness ratio was (ICER) was estimated and compared to threshold values used by payer agencies to guide reimbursement decisions. A cost per quality adjusted life year (QALY) was also estimated for Sweden.

Results. Applying a bidiurnal dosage regimen and using the early tolerisation protocol of Kurnik et al (Haemophilia. 2010;16(2):256–62),prophylaxis was shown to be more effective and less costly (dominant) relative to OD treatment in the UK. In the USA, the model resulted in an ICER - $68,000, which is within the range of treatments reimbursed by third party payers in that country.In Sweden, a cost/QALY of SEK 1.1 million was also within the range of reimbursed treatments in that country, and prophylaxis was dominant over OD treatment when daily dosage was applied. Sensitivity analysis showed that dosage and treatment-induced inhibitor incidence were the most important variables in the model.

Conclusion. Subject to continuing clinical evidence of the effectiveness of pharmacokinetic dosage and the role of prophylaxis in decreasing inhibitor incidence, treatment for life with prophylaxis is a cost-effective therapy, using current criteria for the reimbursement of health care technologies in a number of countries.

Background

Factor replacement remains the mainstay of haemophilia therapy and has resulted in progressive enhancement of life expectancy (LE) and quality of life [1]. In developed countries, a natural progression in haemophilia therapy has been the increasing use of prophylactic treatment with its resultant benefits [2] compared to episodic or on-demand (OD) therapy. Given the high costs of maintaining this therapy, the question arises of continuing prophylaxis regimens established in children as the haemophilia population ages.

When evaluating the clinical and economic impacts of prophylaxis, the emphasis regarding long term outcomes has focused on joint haemarthrosis which affect 95% of patients. However, it is recognised that, in the current era of safe factor concentrates, other types of serious bleeds such as intracranial haemorrhage (ICH) are still responsible for significant morbidity and mortality in haemophilia treated OD. These morbidities are significantly ameliorated when patients are treated prophylactically [3].

Following the elimination of pathogen safety risks, the most significant adverse effect of factor therapy is the development of inhibitors [1]. Recent studies have indicated that patients on early low dose prophylaxis experience a lower incidence of inhibitors than patients on OD [4], possibly as a result of tolerisation to FVIII prior to immunological danger signals [5]. The treatment of inhibitors is very costly , and any modality which influences inhibitor formation will have a significant effect on the cost-effectiveness of haemophilia.

Objective

Assessment of the cost-utility of prophylaxis compared to on-demand treatment in severe haemophilia A treated over a whole lifespan.

Materials & Methods

A cost-utility analysis of haemophilia A treatment was performed over a life time horizon with 100 on year cycles, using a Markov model incorporating health states when using prophylaxis versus OD therapy. The model was applied to two perspectives – the UK National Health Service and of a third party US payer. The primary outcome was the incremental cost per Quality Adjusted Life Year (QALY) gained.

A software package – TreeAge Software, Inc. Williamstown, MA, USA, www.treeage.com - was used to construct a Markov decision model as summarised in **Figure 1**. The model compares two treatment modalities for newly diagnosed previously untreated patients (PUPS): On-Demand (OD) treatment of bleeds and Prophylaxis (Pro) initiated early in the first year of life, envisaged as at the onset of the first soft tissue manifestations of haemophilia and before the onset of joint and life threatening bleeds.

The model has three distinct health states: "**Alive - No Inhibitors**", "**Alive - With Inhibitors**" and "**Dead**". A half cycle correction was applied to avoid overestimating life expectancy. For both OD and Pro arms, a patient starts in the health state "**Alive - No Inhibitors**", and faces a risk of developing inhibitors as a result of the treatment in the first year of life. Depending on the transition probability of inhibitor formation following OD or PRO treatment, Stage 1 of the Markov model was assigned costs for Immune Tolerisation Therapy (ITT).

Depending on the success of ITT (reversion to non-inhibitor state) for both OD and Pro modalities, a patient transitions permanently back to the "**Alive-No Inhibitor**" health state or stays in the "**Alive - With Inhibitor**" health state, for the remaining lifespan until entering the "**Dead**" state.

Within each health state were incorporated clotting factor treatment costs with FVIII for "**Alive - No Inhibitors**" for Pro and OD therapy and with aPCC and FVIIa for "**Alive - With Inhibitors**" for OD and PRO respectively. The costs for major transient clinical events represented in the model by orthopedic surgery and major bleeding events represented by ICH were included.

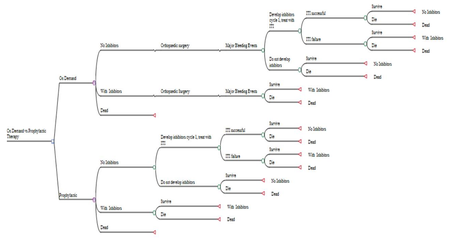
One-way sensitivity analysis (SA) was conducted to check the impact of variables (**Table** 1) considered to be crucial in the model. The variables chosen were FVIII treatment dosages for OD and PRO, cost of FVIII, probability of inhibitor development with prophylaxis and the discount rate for QALYs.

Table 1: Input values for key variables in the model

Parameter	Base Case Values	Ranges for 1-way SA
Utility with Pro	0.9378 – (0.0026*age)	0.82 - 0.92
Utility with OD	0.6705 – (0.0019*age)	0.57 - 0.67
No. of yearly bleeds with Pro	3	0 - 5.4
No. of yearly bleeds with OD	36	10 - 50
Dose with Pro for ages 3-19 years *	59 IU/kg/week	17 - 236 IU/kg
Dose with Pro for ages 20-100 years *	35 IU/kg/week	12 - 119 IU/kg
Dose with OD	35 IU/kg	20 – 50 IU/kg
Cost of FVIII	UK - £0.35	UK - £0.30 - £0.70
	US - $1.00	US - $0.70 - $1.08
Probability of inhibitor development with Pro †	2.5%	0% - 30%
Probability of inhibitor development with OD †	30%	
Discount Rate (QALY)	UK - 3.5% for costs, 1.5% for effectiveness (QALYs)	UK - 0% - 6%
	USA – 3% for costs and effectiveness	US - 0% - 7%

Results

Figure 1: Markov tree



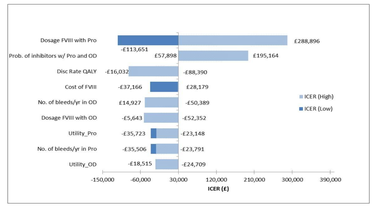
The base case for the two main perspectives studied – the UK and the USA – showed that prophylaxis was either dominant over on-demand therapy (UK)) or generated an ICER which was within the range considered cost-effective (USA). Similar results were obtained for the Swedish perspective (**Table 2**)

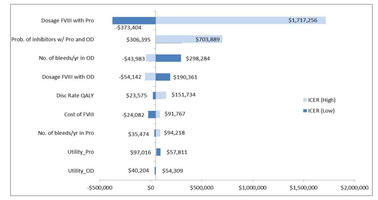
Sensitivity analysis showed that dosage and costs of FVIII were the most important variables influencing the outcomes (**Figure 2**)

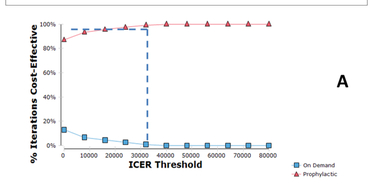
Results (Cont.)

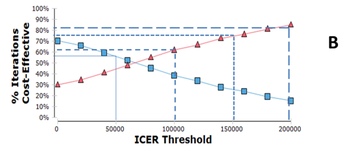
Payer Perspective	Cost	QALYs	Incremental Cost	Incremental QALYs	Cost/QALY	ICER
US						
OD	$4,140,275	19.42	$412,999	6.06	$213,759	$68,109
Pro	$4,563,274	25.48			$179,097	
UK						
OD	£1,784,095	27.16	- £280,866	9.69	£65,688	Dominant
Pro	£1,503,229	36.85			£40,798	
Sweden						
OD	SEK 22,101,124	17.87	SEK 5,331,051	10.99	SEK 1,236,772	SEK 484,888
Pro	SEK 27,432,176	28.87			SEK 950,197	
Sweden (Daily Pro dosing)						
OD	SEK 22,101,124	17.87	- SEK 10,541,993	10.99	SEK 1,236,772	Dominant
Pro	SEK 11,559,131	28.87			SEK 400,386	

⇐Table 2 Outcomes of the decision analysis model









⇑**Figure 2**. One-way Sensitivity Analysis of the key variables affecting the outcome of the Markov model. The Tornado Diagram shows the Incremental Cost Effectiveness Ratio for the variables, showing the results of the upper and lower values included in the analysis in shaded and solid bars respectively. A – UK perspective, B – US perspective

⇐**Figure 3**. Cost Effectiveness Acceptability Curve. The percentages of iterations which are cost effective relative to different ICER thresholds are shown for the two alternative treatments. Prophylaxis is more cost effective than on-demand treatment in the majority of iterations across a wide range of ICERs. Dashed lines show ICER thresholds

Summary

- Incorporating pharamacokinetic dosage and early low dose prophylaxis in the treatment results in prophylaxis being cost-effective relative to on-demand therapy in a range of scenarios
- Although the model discounted benefits at lower rates than costs, as recently recommended for effective chronic treatments, this did not prove crucial in generating these results

Conclusions

- Using clinical interventions which are rapidly emerging as significant contributors to optimal haemophilia therapy, prophylaxis initiated and maintained over the whole of life is shown to be more cost-effective than on-demand therapy in this cost-utility analysis
- Further confirmation through clinical trials of the benefits of pharmacokinetic dosage and early tolerisation protocols is needed to test the robustness of this model
- The approached described can be used to assess the cost-effectiveness of emerging new treatments for haemophilia such as long acting coagulation factors

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