EFFECT OF PHARMACOKINETIC DOSAGE AND INHIBITOR INCIDENCE ON THE COST UTILITY OF LIFE-LONG PROPHYLAXIS IN HAEMOPHILIA A

A. Farrugia [1], M. Bansal [2], J. Cassar [3]

[1]School of Medicine, Australian National University, Canberra, Australia, [2]Global Access, Plasma Protein Therapeutics Association, Annapolis, United States, [3]Faculty of Health, University of Canberra, Canberra, Australia

Introduction

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.

Methods

In the present study, we have performed a cost-utility analysis of haemophilia A treatment 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 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%

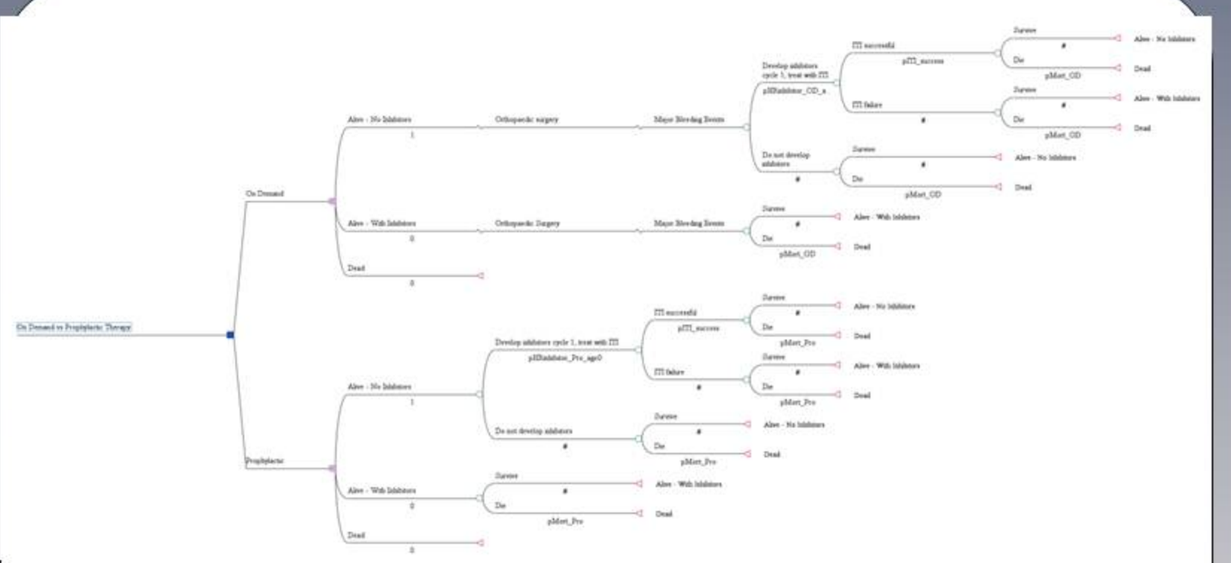

Figure #1: Markov tree

Results

The results of the comparative cost utility analyses are shown in **Table 1**. The model yielded dominance (lower cost for higher QALYs) for prophylaxis versus OD in the UK perspective, and an ICER for prophylaxis versus on-demand of $68,109 for the USA case, primarily because of the higher cost of FVIII in the USA. One-way SA shows that varying the dosage across a range of pharmacokinetic options has the strongest impact on the outcomes of both the UK and the USA cases followed by probability of incidence of inhibitors.

Table #2: Base case results

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	

Table #3: One-way sensitivity analysis results

	UK Perspective			US Perspective		
Parameter	ICER with lower limit	ICER with upper limit	Range of ICER	ICER with lower limit	ICER with upper limit	Range of ICER
Dose of FVIII with Pro for ages 3-100 years	-£113,651	£288,896	£402,547	-$373,404	$1,717,256	$2,090,660
Probability of inhibitor development with Pro and OD	£57,898	£195,164	£137,266	$306,395	$703,889	$397,494
Discount Rate (QALY)	-£16,032	-£88,390	-£72,358	$23,575	$151,734	$128,159
Cost of FVIII	-£37,166	£28,179	£65,345	-$24,082	$91,767	$115,849

Conclusion

Including hitherto unused concepts such as the influence of prophylaxis on inhibitor incidence and the use of pharmacokinetic dosage, the model shows that prophylaxis compared to on-demand treatment results in acceptable cost-effectiveness in conventional pharmacoeconomic terms. Confirmation of these key clinical variables will strengthen this model's potential as a tool for advocacy for the introduction of prophylaxis and its continuation into the adult years

Bibliography

1. Gringeri A, Muca-Perja M, Mangiafico L, von Mackensen S. Pharmacotherapy of haemophilia A. Expert Opinion on Biological Therapy. 2011;11(8):1039–53.
2. Berntorp E, Shapiro AD. Modern haemophilia care. Lancet. 2012;379:1447–56.
3. Witmer C, Presley R, Kulkarni R, Michael Soucie J, Manno CS, Raffini L. Associations between intracranial haemorrhage and prescribed prophylaxis in a large cohort of haemophilia patients in the United States. British journal of haematology. 2011;152(2):211–6.
4. Kurnik K, Bidlingmaier C, Engl W, Chehadeh H, Reipert B, Auerswald G. New early prophylaxis regimen that avoids immunological danger signals can reduce FVIII inhibitor development. Haemophilia. 2010;16(2):256–62.
5. Reipert BM, van den Helden PMW, Schwarz H-P, Hausl C. Mechanisms of action of immune tolerance induction against factor VIII in patients with congenital haemophilia A and factor VIII inhibitors. British Journal of Haematology. 2007 Jan;136(1):12–25.