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ORIGINAL ARTICLE

Factor VIII alloantibody inhibitors: cost analysis of immune tolerance induction vs. prophylaxis and on-demand with bypass treatment

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Summary. Development of inhibitors (alloantibodies to exogenous factor VIII) is the most significant treatment complication in patients with haemophilia A. The only proven way to eradicate inhibitors is through immune tolerance induction (ITI), while bypassing agents are typically employed to treat or prevent bleeds in patients with high titre inhibitors. Costs of these approaches have not been well studied. The aim of this study was to compare lifetime costs of treating patients with severe haemophilia A with inhibitors using on-demand or prophylaxis treatment with bypassing agents and ITI. A decision-analytic model was developed to compare the treatment costs and outcomes. Quantitation of the reduction in bleeding events for patients on prophylaxis and after eradication of inhibitors when on ITI and relapse of inhibitors was derived from published studies. Costs were obtained from standard US costing sources and are reported in 2014 US dollars. Costs and outcomes were discounted 3% per annum. Lifetime costs of treating patients with inhibitors are lower for ITI vs. on-demand or prophylaxis. Patients are also projected to live longer, have greater quality-adjusted life-years, and have fewer bleeding events than patients treated on-demand. Treating patients via ITI to eradicate inhibitors may result in lower lifetime costs and greater life-years and quality-adjusted life-years than treating with bypassing agents.

Keywords: cost-effectiveness, costs, decision model, inhibitors, ITI, prophylaxis with bypassing agents

Introduction

Haemophilia A is the most common severe form of inherited bleeding disorder due to a deficiency of a clotting factor protein, specifically, factor VIII (FVIII) [1]. Individuals with severe haemophilia A are typically diagnosed at an early age (usually in infancy) and have <1% of normal FVIII coagulant activity [2,3]. The most serious complication of treatment for those with severe haemophilia A is the development of FVIII alloantibody inhibitors [2–4]. Alloantibody inhibitors to FVIII are associated with increased mortality and significant morbidity, including a higher rate of bleeding complications, increased disability, and decreased quality of life [5–9].

Three approaches are commonly used to treat such patients with inhibitors: (i) administer bypassing agents such as activated prothrombin complex concentrate (aPCC) or recombinant activated factor VII (rFVIIa) when a bleed occurs (on-demand), (ii) administer bypassing agents prophylactically to prevent bleeds from occurring; or (iii) initiate immune tolerance induction (ITI) with FVIII concentrate to eradicate the inhibitor and then long-term maintenance with a lower dose FVIII prophylaxis regimen to prevent a bleed and to sustain the inhibitor-free status.

Treating haemophilia is expensive at best; however, developing an inhibitor substantially increases those costs. In addition, some treatments may be more costly in the short-term but lead to cost savings in the long-term. As a result, a cost-efficient strategy for treating patients with inhibitors is desirable. In this study, we compare the costs and outcomes of these three treatment approaches in the United States (US) over the course of a patient's lifetime.

Methods

A decision-analytic model was developed in Microsoft Excel. The model is a decision tree (Fig. 1) in which

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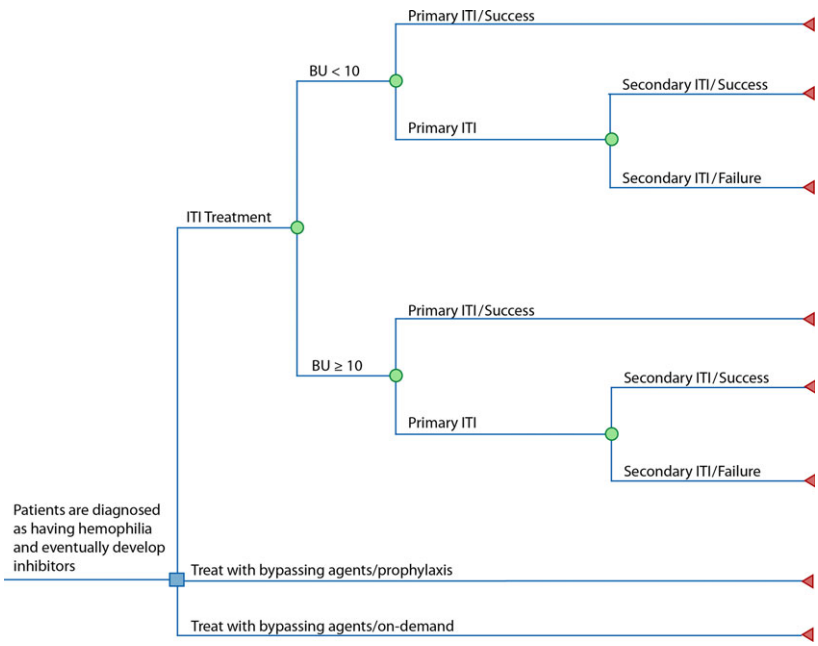

Fig. 1. Model structure. BU = Bethesda unit; ITI = immune tolerance induction.

individuals enter as having newly diagnosed (previously untreated) severe haemophilia A. Data indicate that alloantibody inhibitors develop early in the treatment history (median of 15 exposure days) and affected individuals may be treated by one of three treatments strategies: on-demand therapy, prophylaxis therapy, or ITI. Prophylaxis therapy can be characterized further as primary (initiated after very few bleeding episodes) or secondary (initiated after joint damage is apparent on physical or radiological exam). In this study, primary prophylaxis regimens will be presumed.

Patients treated via primary ITI are classified as good-risk or poor-risk patients as defined by pre-ITI titre levels, as titre levels have been found to affect the likelihood of success and time required to achieve tolerance in the International Immune Tolerance Registry and the North American Immune Tolerance Registry studies [10]. While there are several other factors that may affect the likelihood of success of ITI, such as age, peak historical titre, time since diagnosis of inhibitor before starting ITI, we used as a definition in the model of a good-risk patient being defined as a patient entering ITI treatment with <10 Bethesda units (BU), whereas a poor-risk patient enters ITI with ≥10 BU.

If primary ITI is not successful, then patients will be treated with secondary ITI protocols, which may involve extending the duration of primary ITI, increasing the daily administered dose of FVIII, or switching to a plasma-derived FVIII concentrate that contains von Willebrand factor protein (assuming that primary ITI regimens utilized ultrahigh-purity recombinant FVIII concentrates, which do not contain von Willebrand factor antigen).

If primary or secondary ITI is successful (i.e. inhibitors are eradicated), then patients are treated prophylactically with low-dose FVIII and incur the cost, quality of life, and survival associated with severe haemophilia A in individuals without inhibitors. Patients whose inhibitors are successfully eradicated are at risk of a relapse (i.e. inhibitors return).

Those for whom secondary ITI failed are treated prophylactically with bypassing agents, similar to patients with inhibitors, and incur the costs, quality of life, and impact on mortality that is associated with patients who have alloantibody FVIII inhibitors.

Over the course of the model, patients experience bleeds at rates that are consistent with those observed in published clinical trials. As a cumulative result of these bleeds, patients may eventually require orthopaedic surgery.

Patients are followed over the course of their lifetime in this model, and because replacement therapy and bypass drug dosing is based on weight, patient weight is adjusted longitudinally based on average weight of US males over time, as ascertained in the general population included in the National Health and Nutrition Examination Survey (NHANES) [11].

The perspective of this health economic analysis is that of a third-party payer such as a managed care organization, Medicare/Medicaid, or similar payer. Costs were obtained from standard US costing sources. Costs and outcomes are discounted at 3% per annum.

Patient population

Patients enter the model as infants after diagnosis of haemophilia and are followed for the remainder of their lifetime. Specifically, severe haemophilia A is assumed to be diagnosed at an average age of

2.1 months, with an average weight of 4.9 kg [11,12]. Treatment until inhibitors are diagnosed is assumed to be similar across the treatment approaches. When inhibitors develop, they are assumed to develop at the age of 15.0 months, where patients had an average weight of 10.3 kg [11,13]. Patients are assumed to be similar to patients in Hay and DiMichele [13], with inhibitors at a peak historical inhibitor of $\geq$5 BU mL^{-1} and $\leq$200 BU mL^{-1}, with a starting titre $\leq$10 BU mL^{-1} before randomization, and at age <8 years at the time or randomization in their study.

Comparators

Costs and outcomes were estimated for patients undergoing one of three treatment approaches:

On-demand. Patients were treated for each acute bleeding event with a conventional dose of rFVIIa (a mean of 105 μg kg^{-1}) administered every 2–3 h until the bleed stopped [14]. Patients remained on this treatment for the remainder of their lifetime.

Prophylaxis with bypassing agents. Patients were treated prophylactically with 85 IU kg^{-1} of aPCC three times per week [15]. Patients remained on this treatment for the remainder of their lifetime.

ITI. Patients were treated with 180 μg kg^{-1} of FVIIa daily prior to initiating ITI therapy in an attempt to allow BU to recede to <10. After an appropriate duration of treatment (Table 1), patients were treated with a high-dose ITI regimen of 200 IU kg^{-1} daily of FVIII concentrate. This treatment was selected as the treatment of choice for primary ITI because it was shown in the International Immune Tolerance Induction study to result in more rapid induction of immune tolerance with fewer breakthrough bleeds [13].When ITI was successful, FVIII was resumed at a prophylactic dose (30 IU kg^{-1} FVIII three times per week) for the remainder of the patient's lifetime. When ITI was not successful, patients received secondary ITI in which they continued the high-dose treatment for another 140 weeks. Patients for whom secondary ITI failed received treatment similar to patients receiving prophylaxis with bypassing agents for the remainder of their lifetimes.

Treatments, dosing and durations for each type of patient are presented in Appendix S1 (Figure A-1).

Bleeding events

Clinical effect of bypassing and ITI treatments is based on their impact on bleeding events (Table 1). Without treatment, the annual number of bleeds was estimated from Leissinger *et al*. [15] who reported the mean number of bleeding events in patients with inhibitors during the 6-month on-demand period during the trial as 13.1. We estimated the annual number of minor bleeds to be 26.2. The proportion of bleeds categorized as major was estimated from the clinical guidelines, which reported the approximate frequency of other major bleeds in alloantibody FVIII inhibitor patients as 5% to 10% and central nervous system bleeds as <5% [2]. As a result, we estimated the annual number of major bleeds to be 2.6 (26.2 × 10%). Minor/moderate bleed annual frequency is estimated as 23.6 [26.2 × (1–10%)].

By definition, on-demand treatment had no effect on the number of bleeding events that occurred in a patient. Rather, clinical effect was based on the mean number of infusions that were required to stop the bleeding, which was assumed to be 2.4 (range: 1–8) infusions of rFVIIa for mild/moderate bleeds [14].

Table 1. Base-case clinical efficacy and plausible ranges.

Model parameter	Base-case value	Range	Source/assumption
Weeks post inhibitor diagnosis until start of ITI therapy			
Good risk (BU <10)	24	±20%	DiMichele *et al*. [10]
Poor risk (BU ≥10)	72	±20%	DiMichele *et al*. [10]
Bleeding events			
Annual number minor bleeds	23.6	±20%	Leissinger *et al*. [15]
Annual number major bleeds	2.6	±20%	Leissinger *et al*. [15]; Srivastava *et al*. [2]
Treatment for bleeds			
During ITI therapy with rFVIIa	2.3	±20%	Astermark *et al*. [14]
During prophylaxis bypassing therapy	1.3	1–4	Astermark *et al*. [14]
Primary ITI response			
Good risk (BU <10)	83.1%	±20%	DiMichele *et al*. [10]
Poor risk (BU ≥10)	50.0%	±20%	
Secondary/rescue ITI response			
Good risk (BU <10)	73.7%	±20%	Aledort *et al*. [16]
Poor risk (BU ≥10)	73.7%	±20%	
Relapse after successful ITI			
Relapse rate	15.0%	±20%	Mariani *et al*. [17]
Follow-up years	15	±20%	
Reduction in bleeding events due to prophylactic therapy	61.8%	±20%	Leissinger *et al*. [15]
Reduction in bleeding events during ITI therapy	81.5%	±20%	Manco-Johnson *et al*. [18]

Prophylaxis treatment with bypassing agents has been shown to reduce the number of bleeds that may occur. This reduction in bleeding events was obtained from Leissinger *et al.* [15], where the reported annual mean number of bleeding events during prophylaxis was 5 compared to 13.1 during the on-demand period, representing a 62% reduction in the number of bleeding events.

When bleeding events did occur, patients were assumed to be treated with additional doses of aPCC (see Appendix S1 (Figure A-2) for bleeding treatments). The default daily dosing for aPCC was estimated to be 85 IU kg^{-1} [15]. The number of infusions required to stop the bleeding was assumed to be a mean of 1.3 (range: 1–4) [14].

Manco-Johnson *et al.* [18] reported the mean number of bleeds for patients receiving on-demand treatment and prophylaxis with FVIII to be 17.69 ± 9.25 and 3.27 ± 6.24 per year respectively. This translates to an 81.5% reduction in bleeding events. Given that patients on ITI are essentially receiving prophylaxis with FVIII (Table 1), patients were assumed to observe a reduction of 81.5% in bleeding events while on this prophylaxis during the pre-ITI, ITI and post-ITI periods. Therapy for bleeding events during ITI therapy with rFVIIa for 2.3 doses at a dose of 90 μg kg^{-1} was obtained from Lloyd Jones *et al.* [19], who summarized two studies examining the control of bleeds during ITI. Pre-ITI and post-ITI, regardless of successful eradication of inhibitors, patients were assumed to be treated for bleeding events just as patients who received prophylaxis with bypassing agents.

Response to ITI

Prior to ITI, patients typically are treated as necessary with rFVIIa in an attempt to allow the patient's BU to recede spontaneously to an optimal treatable level. At the start of ITI therapy, 59.7% and 40.3% of patients were assumed to have BU <10 (good-risk patients) and BU ≥10 (poor-risk patients) respectively. This risk distribution was observed among the populations evaluated in the International and North American Immune Tolerance registries [10].

The primary ITI regimen response is estimated as the average successes/failures for each BU level reported in the International and North American Immune Tolerance registries (Table 1) [10]. Good-risk patients responded 83.1% of the time, and poor-risk patients responded 50.0% of the time. Response for patients receiving secondary/rescue ITI was obtained from Oldenburg *et al.* [20], who reported a response rate for complete and partial success to be 73.7% (14 patients responded of the 19 that initiated rescue ITI). Even though all patients had a BU ≤10, they were considered as a whole to be at increased risk of failure of ITI. We chose to categorize risk in the rescue population similar to the good-risk population in the model. As the response rate was not reported for the different risk levels and due to all patients having BU levels ≤10 at the start of rescue ITI, we assumed the response would be the same among the risk levels. Spontaneous clearance of inhibitors was assumed to not occur in the model. Additional, based on DiMichele *et al.* [10], no data support the superiority of any FVIII product. Therefore, we assumed the same success rates among plasma-derived and recombinant FVIII products.

Inhibitor relapse

Relapse after successful ITI was obtained from Mariani *et al.* [17] who state "the risk of relapse was approximately 15% after 15 years of follow-up." Patients who experienced a relapse were assumed to be treated with the same prophylaxis as patients with inhibitors (aPCC).

Orthopaedic surgery

The percentage of patients receiving surgery was based on the number of target joint bleeds that a patient incurs. The percentage of bleeds that were estimated to occur in target joints was 53.6% [21]. Fischer *et al.* [22] present an algorithm in which a patient's Pettersson score increases by 1 point for every 12.6 target joint bleeds. Patients who achieved a Pettersson score of 28 (threshold for clinically relevant damage) were assumed to require surgery. No joint replacement surgeries were performed after patients reached 80 years of age.

Mortality

Individuals with haemophilia have been shown to have a life expectancy similar to males without haemophilia [23]. As a result, life expectancy for our modelling for patients with haemophilia without inhibitors was obtained from the National Vital Statistics System from the Centers for Disease Control and Prevention and the National Center for Health Statistics [24].

Given the limited availability of data and the preference for relative risk data, we have assumed an increased mortality due to inhibitors to be 1.6. [25]. Patient life expectancy and relative risk were combined when inhibitors were estimated to be present in order to derive the overall life expectancy of patients on the different treatments.

Costs

Modelled costs included drug acquisition costs to treat bleeds and to treat haemophilia prophylactically to

prevent bleeds (Table 2). In addition, major bleeds were treated via hospitalization at a cost of $30 890 [26,27]. Orthopaedic surgery was estimated at $41 800 [27–29]. All costs are reported in 2014 US dollars.

Utility weights

Utility weights for patients without inhibitors while receiving on-demand treatment and while receiving prophylaxis were estimated at 0.62 and 0.87 respectively [33]. Patients with inhibitors were reported to have a utility weight of 0.79. In our analysis, utility weights were assumed to be multiplicative. As a result, patients with inhibitors while on prophylaxis were estimated to have a utility weight of 0.68.

Model calculations

For each treatment strategy, we derived lifetime drug and hospitalization costs, bleeding events, life-years, quality-adjusted life-years (QALYs) and the incremental cost per QALY gained. The incremental cost per QALY gained or incremental cost-effectiveness ratio (ICER) is calculated as (total costs of treatment strategy 1 – total cost of treatment strategy 2)/(total QALYs for treatment strategy 1 – total QALYs for treatment strategy 2). The ICER was compared to willingness-to-pay thresholds of $50 000 and $100 000. A threshold of $50 000 is the most common threshold for denoting a treatment is cost-effective in the US; however, some have argued that $50 000 is too low. Thus, we also present cost-effectiveness at thresholds of both $50 000 and $100 000 [34].

In this analysis, treatment strategy 1 was either prophylaxis with bypassing agents or ITI, and treatment strategy 2 was on-demand treatment.

Sensitivity analyses

To test the robustness of model assumptions and parameters, we examined the effect of changing parameters in one-way and probabilistic sensitivity (second-order Monte Carlo simulation) analyses. For one-way sensitivity analyses, parameters were ranked from most sensitive to least sensitive and plotted in the form of a tornado diagram.

Scatter plots were developed to graphically show uncertainty in the probabilistic sensitivity analysis.

Results

Base analysis

Treating patients with inhibitors via ITI can successfully eradicate the inhibitors 69.8% of the time. Patients treated via ITI or prophylactically with bypassing agents, respectively, incurred approximately 77% and 61% fewer bleeding events over their lifetime compared to patients treated via on-demand therapy (Table 3). In addition, patients treated via ITI were projected to live 4.3 years longer than patients on prophylaxis and on-demand therapy and have 4.3 and 9.9 more QALYs than patients on prophylaxis and on-demand therapy respectively. As a result, the estimated lifetime costs of treating patients with inhibitors was lower for ITI compared with either on-demand treatment or prophylaxis with bypassing agents. ITI is cost-saving (i.e. less costly and more effective in terms of reducing bleeding events and increasing QALYs).

ITI therapy is associated with higher costs early on when inhibitors occur. In a breakeven analysis (Fig. 2), the costs of successful ITI became equivalent to prophylaxis after 9 years and then became dramatically less than the costs of prophylaxis with bypassing

Table 2. Base-case costs and plausible ranges.

Model parameter	Base-case value	Range	Source/assumption
Drug costs			
pdFVIII (per IU)	$0.77	±20%	FFF Enterprises [30]
rFVIII (per IU)	$1.07	±20%	FFF Enterprises [30]
aPCC (per IU)	$1.55	±20%	FFF Enterprises [30]
rFVIIa (per μg)	$1.53	±20%	FFF Enterprises [30]
Factor inhibitor test (per test)	$17.55	±20%	AMA [31]; RBRVS using CPT codes 85335 [32]
Hospitalization for major bleed	$30 890	$24 712–$37 068	HCUP [26]; BLS [27]
Arthropathy surgery	$41 800	$33 440–$50 160	HCUP [29]; BLS [27]; assumes average of hip and knee replacements as seen in Knight *et al.* [28]
Inhibitor monitoring			
Frequency for inhibitor eradication (quarterly)	1	0.25–3.0	WFH Guidelines [3]
Frequency for inhibitor recurrence (quarterly)	1	0.25–3.0	WFH Guidelines [3]
Duration of monitoring for inhibitor recurrence after tolerance achieved	12	±20%	Hay and DiMichele [13]

pdFVIII indicates plasma-derived factor VIII; rFVIII, recombinant factor VIII; AMA, American Medical Association; RBRVS, Resource-Based Relative Value Scale; CPT, Current Procedural Terminology; HCUP, Healthcare Cost and Utilization Project; BLS, Bureau of Labor Statistics; WFH, World Federation of Hemophilia.

Table 3. Base-case results.

	ITI	On-demand	Prophylaxis
Drug and hospitalization cost (discounted)	$19 904 815	$21 562 055	$43 106 359
Life-years (projected)	74.5	70.3	70.3
QALYs (discounted)	24.9	14.9	20.5
Bleeding events (projected)	427	1828	718
Difference in ITI and on-demand or prophylaxis costs	–	−$1 657 240	−$23 201 543

agents; whereas it took 20 years for ITI therapy to become equivalent to on-demand therapy with bypassing agents before it became less costly.

Sensitivity analysis

In comparing treatment via ITI with prophylaxis, one-way sensitivity analysis (Fig. 3a) showed that results were sensitive to changes in the percentage of patients with BU <10, inhibitor utility weights, and the discount rate for costs and outcomes. However, the direction of the results did not change when varied within its plausible range. Results were found to be insensitive to changes in all other parameters including changes in dosing.

The ICER for ITI compared with on-demand treatment (Fig. 3b) was sensitive to changes in the cost per microgram of rFVIIa, annual number of minor bleeds, percentage of patients with BU <10, discount rate for costs, number of aPCC doses to stop bleeding events when on prophylaxis, and cost per international unit of aPCC. Specifically, as the number of aPCC doses to stop bleeding events when on prophylaxis increased to its upper bound and the cost per microgram of rFVIIa and annual number of minor bleeds decreased to their lower bound, ITI was not cost-effective assuming a willingness-to-pay threshold of $100 000 per QALY gained. ITI no longer remained cost-saving when increasing the percentage of patients with BU <10, the discount rate for costs, and the cost per international unit of aPCC; however, ITI remained cost-effective (ICER <$50 000). Results were found to be insensitive to changes in all other parameters, including changes in dosing in the other treatments.

Probabilistic sensitivity analysis showed that ITI was cost-saving 84.4% of the time and was cost-effective (ICER ≤$50 000) 100.0% of the time compared with prophylaxis (Fig. 4a). In comparing ITI with on-demand treatment, probabilistic sensitivity analysis showed that ITI was cost-saving 52.7% of the time and was cost-effective 61.1% (ICER ≤$50 000) and 63.9% (ICER ≤$100 000) of the time (Fig. 4b). However, the reader should review these analyses carefully as the figures show a fair amount of uncertainty, as a result of the limited availability of information around the correlation of parameters and their values.

Discussion

In this study, we developed a decision-analytic model to compare the lifetime costs of using ITI treatment to

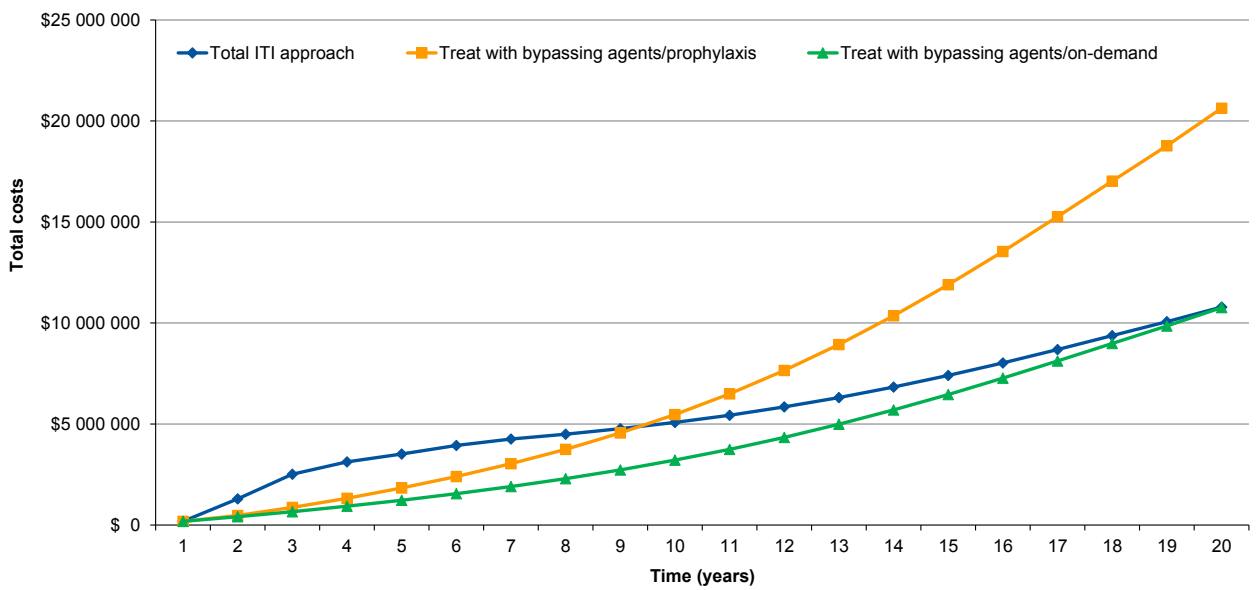

Fig. 2. Cumulative Costs Over Time for Patients Treated via ITI, Prophylaxis, and On-demand Treatment. The dark grey line with diamonds represents the cumulative cost of a patient who is treated via the ITI approach; the black line with squares represents the cumulative cost of a patient who is treated prophylactically with bypassing agents; and the light grey line with triangles represents the cumulative cost of a patient who is treated via the on-demand approach. ITI = immune tolerance induction.

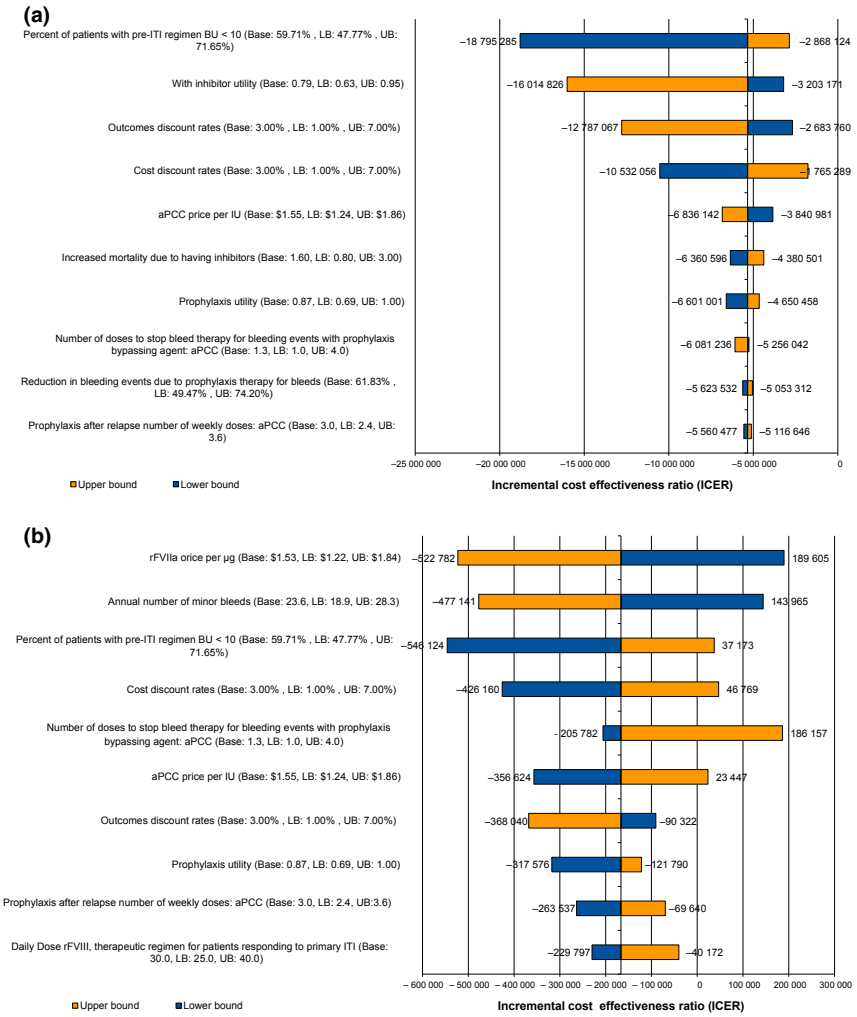

Fig. 3. One-way Sensitivity Analysis Results: ITI vs. Prophylaxis and ITI vs. On-demand Treatment. (a) presents results of the one-way sensitivity analysis of treating via ITI compared with treating via prophylaxis. Dark-shaded bars represent the upper bound value of the parameter. Light-shaded bars represent the lower bound value of the parameter. Baseline incremental cost per QALY on the *x*-axis is −$5 338 561. (b) presents results of the one-way sensitivity analysis of treating via ITI compared with treating on-demand. Dark-shaded bars represent the upper bound value of the parameter. Light-shaded bars represent the lower bound value of the parameter. Baseline incremental cost per QALY on the *x*-axis is −$166 588. aPCC = activated prothrombin complex concentrate; BU = Bethesda unit; ITI = immune tolerance induction; IU = international unit; LB = lower bound; rFVIIa = recombinant activated factor VII; rFVIII = recombinant factor VIII; QALY = quality-adjusted life-year; UB = upper bound.

eradicate inhibitors with those of using on-demand treatment or prophylaxis with bypassing agents. To our knowledge, a comparison of these three treatment approaches in the same analysis has not been performed. The decision model follows patients from haemophilia diagnosis until death. Evidence from published clinical trials and registries was used to inform the decision process.

The model showed that treating haemophilia patients with inhibitors is costly regardless of the preferred treatment approach. In particular, although ITI treatment is associated with a high cost, the overall costs are substantially lower than treating prophylactically with bypassing agents. The breakeven point for treating with ITI compared with prophylaxis is 9 years, of which an average of 2 years occurs before ITI therapy can begin. ITI is also associated with an increase in life expectancy in addition to a reduction in bleeding events. Results were sensitive to patient BU levels (defining characteristic for good risk vs. poor risk) and patient preferences for inhibitors when compared with prophylaxis. However, even if a patient was a poor-risk patient and having inhibitors did not affect the patient's quality of life, costs would still be substantially lower when treating via ITI. When compared with on-demand treatment, ITI was found to be less costly, though not substantially so. As a result, when the price per microgram of rFVIIa and the annual number of minor bleeds approached their lower bounds, ITI was found to no longer be cost-effective at a willingness-to-pay threshold of $100000 per QALY gained. However, on-demand treatment carries substantially more risks due to the occurrence of four times as many bleeding events, which significantly affects patient quality of life. As expected, results were sensitive to changes in drug costs and number of bleeding events.

This study is unique in comparison to prior modelled health economic studies in inhibitor patients because it analysed all patients from time of diagnosis according to the International Immune Tolerance Induction study and took advantage of more recent

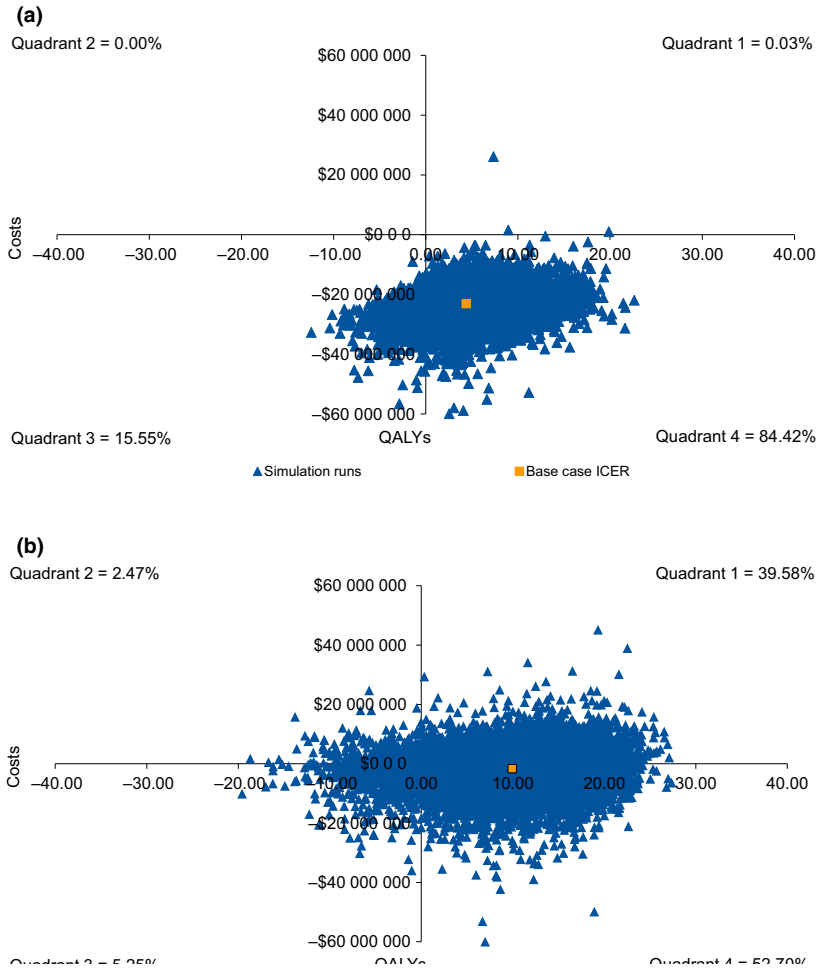

Fig. 4. Probabilistic Sensitivity Analysis Scatter Plots: ITI Versus Prophylaxis and ITI vs. On-demand Treatment. (a) presents results of the probabilistic sensitivity analysis of treating via ITI compared with treating via prophylaxis. Grey dots represent results of 10 000 runs of the model with varying input data. The black square dot represents the base-case run of the model. (b) presents results of the probabilistic sensitivity analysis of treating via ITI compared with treating on-demand. Grey dots represent results of 10 000 runs of the model with varying input data. The black square dot represents the base-case run of the model. ICER = incremental cost-effectiveness ratio; ITI = immune tolerance induction; QALY = quality-adjusted life-year.

clinical data, which fine-tuned age of inhibitor diagnosis, success of ITI for various therapeutic strategies, breakthrough bleeding statistics, and rates of inhibitor relapse. This analysis is perhaps most similar to the analysis reported by Colowick *et al.* [35] in which haemophilia patients with inhibitors were treated with either an on-demand or a low-dose (100 IU kg day^{-1}) ITI approach. Colowick *et al.* [35] accounted for the different types of bleeding events (mild, moderate, and major) and occurrence of orthopaedic surgery as we did. However, their analysis only considered drug cost. In another analysis, Knight *et al.* [28] compared ITI with an on-demand approach from a United Kingdom (UK) perspective, specifically the treatment of various ITI and on-demand protocols. Since their analysis was from the UK perspective, resulting costs were difficult to compare. In a more recent analysis by Farrugia *et al.* [36], treatment of haemophilia with an on-demand and prophylaxis approach was examined. If inhibitors developed, patients were then treated with ITI. Results were presented for a United Kingdom, US, and Swedish perspective where patient characteristics (i.e. age, body weight, bleeding rates, probability of developing inhibitors and mortality) and treatment were assumed the same between countries. Although Farrugia *et al.* [36] examined different treatment strategies, QALYs were found to be similar between the two analyses when accounting for utility differences.

It is important to note that none of the previous health economic studies considered secondary ITI or the potential for inhibitor relapse in patients treated via ITI. ITI is considered a costly treatment. When use of secondary ITI is considered upon failure of primary ITI, patient costs will increase. As a result, we feel the analysis presented here provides for a more comprehensive consideration of inhibitor treatment costs over a patient's lifetime.

One limitation of this study is that the analysis examined the impact of one ITI dose protocol. In reality, haemophilia treatment centres utilize different ITI protocols. As a result, decision-makers may not consider this analysis applicable to their situation. For this analysis, we chose to examine a high-dose protocol

for ITI (daily use of 200 IU kg^{-1}). We chose this dose because it is a dose upon which the most comprehensive information exists in relation to primary and secondary ITI [10,13]. In addition, more frequent bleeding was reported to occur in the low-dose arm of the International Immune Tolerance Study [13]. Regardless of dose used in clinical practice, we believe the results of this study are important for treatment centres using different ITI protocols, because other ITI protocols tend to use lower doses. Because drug costs are a primary driver of the overall costs, the results of this analysis may be considered conservative for centres using lower dose protocols. In fact, running the analysis with an ITI daily dose of 100 IU kg^{-1} resulted in a total cost of $18 957 325 for ITI ($2 604 730 lower than on-demand and $24 149 034 lower than prophylaxis), with a breakeven point of 7 years for treating with ITI compared with prophylaxis, of which an average of 2 years occur before ITI therapy can begin.

Another limitation of this analysis for comparing ITI and prophylaxis approaches with on-demand treatment is the limited availability of patient preference data in the form of utility weights. The utility weights for this analysis were obtained from a survey of patients with severe haemophilia with/without inhibitors treated via an on-demand or prophylaxis approach [33]. The authors attempted to examine quality of life differences in patients with/without inhibitors. However, sample sizes were small. The development of inhibitors essentially makes the treatment of bleeding events more difficult. As a result, if quality of life for patients with/without inhibitors could be obtained based on bleeding events, perhaps a larger impact on patient preferences for treatment might be estimated. Understanding the differences in quality of life in patients with/without inhibitors will be important for understanding the ultimate value of the different treatment approaches to patients.

Decision-makers may also consider our assumption around mortality to be an additional limitation. We assumed that haemophilia patients with no inhibitors experienced survival similar to the general population and that patients with inhibitors experienced an increased risk of mortality. Specifically, we assumed an additional risk of 1.6 for patients with inhibitors [25]. This may be noted as high. However, odds of death for patients with inhibitors have been reported to be 1.7 in more recent analyses [37]. Previous economic analyses have assumed higher increases in this risk [28,35]. Furthermore, sensitivity analysis examining the impact of the increased risk of death for patients with inhibitors was found to have little impact on the differences in costs when comparing ITI with on-demand treatment.

Conclusion

Overall, treating patients with inhibitors is costly. However, costs may be controllable without sacrificing clinical benefit. In fact, clinically beneficial treatments may be less costly than perceived. Specifically, ITI provides not only a clinical benefit in terms of eradication of inhibitors, reduction of bleeding events, and improved QALYs, but it may come at a more reasonable cost. Of course, further research will be important for validating these results.

This economic assessment can provide physicians, payers and other decision-makers with valuable information that is systematically compiled in a mathematical format based on recent clinical evidence to predict the economic consequences and individual benefits of novel bypass products and therapeutic strategies for the care of individuals with alloantibody FVIII inhibitors. This is important as we continue to learn about the potential utility and immunogenicity of the prolonged half-life rFVIII products, the human cell line–derived B-domain–deleted FVIII concentrate, and the eventual implementation of FVIII mimetic therapies.

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Disclosure

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Supporting Information

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

Appendix S1. Mortality, Utilities and Sensitivity Analyses Supporting Appendix.

