

REVIEW ARTICLE

Cost of care of haemophilia with inhibitors

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Summary. In Western countries, the treatment of patients with inhibitors is presently the most challenging and serious issue in haemophilia management, direct costs of clotting factor concentrates accounting for >98% of the highest economic burden absorbed for the healthcare of patients in this setting. Being designed to address questions of resource allocation and effectiveness, decision models are the golden standard to reliably assess the overall economic implications of haemophilia with inhibitors in terms of mortality, bleeding-related morbidity, and severity of arthropathy. However, presently, most data analyses stem from retrospective short-term evaluations, that only allow for the analysis of direct health costs. In the setting of chronic diseases, the cost-utility analysis, that takes into account the beneficial effects of a given treatment/healthcare intervention in terms of health-related quality of life, is likely to be the most appropriate approach. To calculate net benefits, the

quality adjusted life year, that significantly reflects such health gain, has to be compared with specific economic impacts. Differences in data sources, in medical practice and/or in healthcare systems and costs, imply that most current pharmacoeconomic analyses are confined to a narrow healthcare payer perspective. Long-term/lifetime prospective or observational studies, devoted to a careful definition of when to start a treatment; of regimens (dose and type of product) to employ, and of inhibitor population (children/adults, low-responding/high responding inhibitors) to study, are thus urgently needed to allow for newer insights, based on reliable data sources into resource allocation, effectiveness and cost-utility analysis in the treatment of haemophiliacs with inhibitors.

Keywords: cross-utility analysis, decision models, haemophilia, inhibitors, pharmacoeconomy, quality of life

Introduction

In developed countries, where economic resources are available for high-cost products, the development of antibodies neutralizing the haemostatic effect of therapeutically administered clotting factor concentrates (inhibitors) is the key problem of treating haemophilia [1]. In the presence of an inhibitor, especially if at high-titre, the standard

safe and effective replacement treatment is hampered, and high rates of morbidity and mortality are reported [2]. In addition, this challenging treatment is associated with a very high economic burden [3,4]. At variance with other settings of chronic disease, costs of treatment in haemophilia are mainly related to direct costs of replacement clotting factor concentrates [4,5]. When patients with inhibitors are evaluated, these costs account for more than 98% of the strikingly high amount of medical and economic resources absorbed for their care [4].

In the era of safe plasma-derived and recombinant products and of prophylaxis to prevent arthropathy, the impact of which should be evaluated in a long-term or life-long perspective, a pharmacoeconomic approach is a complex task. This is maximally true in haemophilia patients with inhibitors: being inhibitor

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development a relatively rare complication of a rare disease, available data are rather limited. Taking into account the different leading characters of the health-care process, different readings are conceivable: the patients and their caregivers stress the clinical problems and their impact in the daily life; the medical professionals emphasize the cost of the health-care system; the health-care payer pays attention to directly or indirectly absorbed resources. All these readings should be actualized in a specific social tissue, with time- and region (country)-specific analyses (Table 1) [6].

Managing haemophilia with inhibitors: current strategies

The development of a specific inhibitor to factor VIII (FVIII) or factor IX (FIX) results in partial or complete lack of efficacy of clotting factor concentrates. Because of the wide clinical variability and responsiveness to current therapeutic approaches and, in turn, because of the lack of studies providing high-level evidence for *ad hoc* guidelines, current

strategies for managing these patients are rather heterogeneous. In patients with transient or low-responding inhibitors or with low actual inhibitor titre ($<5 \text{ BU mL}^{-1}$), bleeding episodes are commonly managed by increasing dosages of FVIII/FIX concentrates. In contrast, in the majority of patients with high-responding inhibitor titres, by-passing agents (recombinant activated factor VII, rFVIIa; activated prothrombin complex concentrates, aPCC) are needed (Fig. 1). Different regimens of treatment (dosing, scheduling of administration) and clinical outcomes are reported in this setting [7,8]. Anecdotal reports [8,9] suggest improved efficacy by combining (or employing sequentially) rFVIIa and aPCC. For both agents, data are also being collected on the effectiveness of prophylactic regimens for patients with life-threatening or highly frequent bleeds.

Given the serious clinical consequences of inhibitors, immune tolerance induction (ITI) to eradicate inhibitors and restore standard factor concentrate treatment and prophylaxis feasibility (Fig. 1) is attempted in most patients with inhibitors, especially in children, as soon as possible after diagnosis

Table 1. Cost of care in everyday's life of haemophilia with inhibitors: definitions.

Resource allocation	The manner in which (scarce) resources are distributed. From a business standpoint, this relates to how management distributes capital among its various operations. From a consumer's viewpoint, resource allocation relates to how goods and services are distributed among consumers.
Effectiveness, Efficiency	Degree to which objectives are achieved and the extent to which targeted problems are solved. In contrast to efficiency, effectiveness is determined without reference to costs: whereas efficiency means 'doing the thing right,' effectiveness means 'doing the right thing.'
Decision models	Systematic approach to collecting facts and applying logical decision making techniques, instead of generalizing from experience, intuition (guessing), or trial and error.
Cost/utility analysis	A technique designed to determine the feasibility of a project or plan by quantifying its costs and benefits. The cost/ success ratio is an application of such definition
Health-related quality of life (HRQoL)	Public health professionals use HRQoL to measure the effects of numerous disorders, short- and long-term disabilities, and diseases in different populations. Physicians have often used HRQoL to measure how a chronic illness interferes with a person's day-to-day life.
Quality adjusted life year (QALY)	A measure of disease burden, including both the quality and the quantity of life lived. It is used to assess the value for money of a medical intervention. The QALY is based on the number of years of life that would be added by the intervention. Each year in perfect health is assigned the value of 1.0, death is assigned a value of 0.0. If the extra years would not be lived in full health, (e.g. if the patient would be confined to a wheelchair), the extra life-years are given a value between 0 and 1.
Threshold incremental cost-effectiveness ratio [ICER (λ)]	The value of cost per QALY, plays a pivotal role in cost-effective analysis. Some analysts argue that ICER represents the willingness of a society to pay for additional QALYs. Others argue that such threshold leads to uncontrolled expenditure growth when new procedures deliver QALYs at less than the threshold.

Note: With the exception of QALY (Wikipedia, the free encyclopedia) and of HRQoL (US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion), all other definitions are based on The American Heritage® Dictionary of Business Terms 2009, Copyright by Houghton Mifflin Harcourt Publishing Co. The concept of ICER is further analyzed in references [48,49].

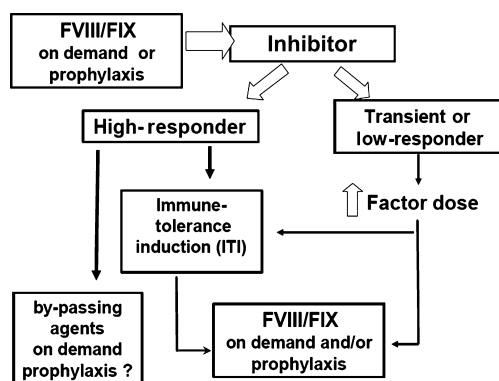


Fig. 1. Current treatment approaches for patients with haemophilia A with inhibitors.

[7–11]. However, therapeutic protocols of such strategy (dose/type of concentrate, interval of infusions, association with immunomodulating agents) dramatically differ [7,8].

Methods

We have approached the issue of: cost of care in everyday’s life of haemophiliacs with inhibitors, with emphasis on three comprehensively reviewed relevant issues:

1. The actual impact and the wide inter-individual variability of costs of care in patients with inhibitors. This issue, addressed in several studies, has been prospectively analyzed by Gringeri *et al.* [12].
2. rFVIIa vs. aPCC for the on-demand treatment of bleeding episodes. This issue has been thoroughly reviewed by Lyseng-Williamson and Plosker in 2007 [13] and by Knight *et al.* in 2009 [14].
3. The lifetime evaluation of cost-effectiveness of different strategies of treatment of patients with high-responding inhibitors. Three immune tolerance induction protocols and on one on-demand

Table 2. Characteristics of the studies reviewed (see ‘Methods’ section for details).

Reference	Type of study	Type of patients, <i>n</i>	Inhibitors	Source of costs evaluated	Country, years
[16]	Retrospective	145, 41 with inhibitors, adults and children	HR 41%	Concentrates(cost per patient/yr)	France, 1988–1995; 1996–1998
[17]	Retrospective, case-control	18, nine with inhibitors, adults and children	HR	Concentrates (cost per patient/year, 3.5 year follow-up)	Canada, 1988–1993
[32]	Extrapolated from the IITR	128, adults and children	HR & LR	Concentrates (cost per 50% ITI success)	USA, 1999
[35]	Decision model	Children, lifetime	HR	Concentrates, lifetime (ITI vs. on demand treatment)	USA, 1999
[20]	Retrospective -prospective	6 children	HR	Direct healthcare costs (per patient/yr)	Australia, 1998–1999
[21]	Decision model	NR	NR	Concentrates (cost per resolved bleed)	UK, 1999–2000
[12]	Prospective	52, adults	HR 98%	Direct healthcare costs (per patient/mo, 18-month follow-up)	Italy, 1998–1999
[15]	Decision model	Children, lifetime	HR	Direct healthcare costs, cost-utility analysis, life time (different on-demand and ITI regimens).	UK, 2001
[18]	Retrospective	12, adults and children	HR 25%	Concentrates (cost per patient/yr)	USA, 1993–1998
[34]	Decision model	Adults and children	HR ~60%	Concentrates (cost per patient/yr)	Germany, 2002
[28]	Decision model	Children	HR	Concentrates (cost per resolved bleed)	US, 2004
[24]	Decision model	Adults	HR	Concentrates (cost per resolved bleed)	US, 2005
[19]	Prospective	58, seven with inhibitors, adults and children	HR	Direct healthcare costs (per patient/yr, 24-month follow-up)	US, 1995–1997
[26]	Decision model	Adults	HR	Concentrates (cost per resolved bleed)	Brazil, 2005

HR, high responding; LR, low responding; NR, not reported.

regimen, already shown to be cost-effective, have been reported in a decision model analysis by Knight *et al.* [15].

For an in-depth scrutiny of the issues/claims provided by the four papers, their references were also critically reviewed (Table 2). In each case and for each report, in addition to clinical relevance, emphasis has been put and the inherent potential limitations of the individual pharmacoeconomic analysis.

The actual impact and the wide inter-individual variability of costs of care in patients with inhibitors (Table 3)

- The issue as a whole has been evaluated in a series of studies [12,16–20], most of which stressing the extremely wide range of individual costs, that reflect an often severe and difficult to handle clinical variability [4,17–19]. Average annual concentrate costs 1.5–3-fold higher in inhibitor patients than in non-inhibitor patients were reported [16–19]. A French retrospective study [16] showed that such difference was mainly due to patients with high-responding inhibitors and that this gap became greater after the entry of rFVIIa in the market (after 1996). In the frame of a general increase of costs of treatment in haemophilia due to the use of recombinant products, whereas mean costs per patient/year in patients with high-responding inhibitors were \approx 1.5-fold higher than in those without inhibitors (59 000 vs. 41 000 US\$) over the 1988–1995 period, these figures become >3-fold higher (60 000 vs. 186 000 US\$) in the 1996–1998 period [16]. The increase in costs attributable to rFVIIa was smaller in a study carried out in Australia (mean cost per patient/year 113 465 vs. 97 988 US\$), in which all health resources absorbed for care of six inhibitor patients with severe arthropathy (clotting factor concentrates, hospitalizations and medical interventions, including psychologist consultancies and physiotherapy cycles) were calculated. Although the latter study involved a very small patient sample, when the quality of life assessment (EuroQoL-5D, EQ5D) was included in the (cost-utility) analysis, rFVIIa treatment was associated with a better QALY than standard treatment (0.48 vs. –0.11). The net incremental cost/QALY (26 684 US\$) appeared to be justified by such improvement [20].
- The ‘outlier issue’ (the mean/median issue). In a retrospective case-control Canadian study, based on the 3.5-year (1988–1993) treatment records of nine inhibitor patients vs. 9 age- and severity-matched non-inhibitor control patients, the annual product cost (mean) was 2.25-fold greater in patients with inhibitors than in those without (226 627 vs. 100 684 US\$, respectively). However, when median values were considered, the difference was strikingly lower (101 431 vs. 89 756). Such discrepancy was explained by the treatment records of a single inhibitor patient, whose costs accounted for 62% of the total inhibitor group. Such higher treatment costs were mainly associated with the use of rFVIIa [17]. Similar data were reported in a larger retrospective cohort study, with a median follow-up of 4.5-years (12 inhibitor patients and 28 age- and severity-matched controls, 184 patient-years), carried out among US patients diagnosed between 1993 and 1998. No rFVII was available at that

Table 3. The actual impact and the wide inter-individual variability of costs of care in patients with inhibitors.

Take home messages.

- General
 - a. >3-fold higher costs of treatment in haemophilia after 1996 due to the use of recombinant products [16].
 - b. Average annual concentrate costs 1.5- to 3-fold higher in inhibitor patients than in non-inhibitor patients [16–19].
 - c. The ‘outlier issue’. Treatment costs of a single or few inhibitor patients account for a very large proportion of the total higher costs of the inhibitor group. Higher treatment costs associated with the use of rFVIIa [17–19].
 - d. Hospital-related costs (59% vs. <10%) [19] at least in part independent of the outliers.

Setting: Pharmacoeconomic analyses from retrospective, short-term evaluations that only allow for the analysis of costs of concentrates and of other direct health costs [16–19].

- The highly expensive care provides a satisfactory quality of life in haemophilia with inhibitors
 - a. Over the 18-month follow-up, no exceedingly high bleeding tendency in inhibitor patients versus those without.
 - b. Monthly cost/patient \sim 18 000 €; \sim 50% of patients require <5000 € per month, only 2% needing >100 000 €.
 - c. 98.8% of the costs of care due to factor concentrates, 47.3% being related to rFVIIa (orthopaedic surgery)
 - d. Hospitalizations mostly due to orthopaedic surgery.
 - e. HRQoL comparable to that of patients without inhibitors.

Setting: COCIS [12] Prospective data picture of costs of care and of quality of life in a large cohort of inhibitor patients (52 high-responder patients, about one-third of the total Italian inhibitor population).

[] = reference[s] of the present report which to refer to for an in-depth analysis of the issue(s).

time. A striking discrepancy was documented between the annual *mean* (141 000 vs. 80 000 US\$) and *median* (55 900 vs. 58 300 US\$) costs of patients with or without inhibitors, also in this case due to the presence of two outliers requiring intensive treatments [18]. A large year-to-year variation and a higher impact of hospital-related costs (59% vs. <10%) is documented in another study [19] in which the wider than normal range of individual annual costs of seven outliers (88 000–2 016 086 US\$) was emphasized. However, cost variability was also true after excluding the outliers, further arguing for the general complex management of bleeds in such patients.

- That this highly expensive care provides a satisfactory quality of life in haemophilia with inhibitors has been prospectively documented by the Italian Cost of Care Inhibitors Study (COCIS) [12]. This survey, carried out between 1998 and 1999, provides a detailed picture of costs of care and of quality of life in a large cohort of inhibitor patients (52 high-responder patients, about one-third of the total Italian inhibitor population). Over the 18-month follow-up, patients did not exhibit an exceedingly high bleeding tendency (0.6 and 0.46 total and joint bleeds per patient/month, respectively). Monthly cost per patient was ~18 000 €, about half of patients requiring less than 5000 € per month, and only 2% needing 100 000 € or more. On the whole, 98.8% of the costs of care were due to clotting factor concentrates, 47.3% being related to rFVIIa (mostly, for orthopaedic surgery). Only 1.2% of expenses was

attributable to visits, surgeries and hospitalizations. As to the latter, about half were due to orthopaedic surgery (six patients underwent joint replacement over the study period). This high number of joint interventions in the short period of time was attributable to previous difficulties in performing such procedures. The huge health costs of these patients were framed by the COCIS Investigators in the context of quality of life of these patients, as evaluated by validated questionnaires (EQ5D, SF-36). Although >80% of patients in this cohort had a severe hemophilia-related disability, their overall HRQoL was comparable to that of patients without inhibitors, and only 4% of them reported 'extreme problems' in one or more dimensions of the EQ-5D profile. Physical rather than mental components dimensions appeared to be affected, the latter being entirely comparable to those of the general population. On the whole, the global perception of HRQoL in inhibitor patients was comparable to that reported in other settings of chronic diseases (e.g. diabetes mellitus dialysis-dependent chronic renal failure).

rFVIIa, vs. aPCC for the on-demand treatment of bleeding episodes (Table 4)

- The costs of the treatment of bleeding with rFVIIa and/or with aPCC in haemophilia patients with inhibitors have been calculated in a series of cost analysis evaluations [13,21–29]. Most studies, addressing a comparison of on-demand treatment of mild or moderate bleeds with rFVIIa vs. aPCC,

Table 4. rFVIIa, vs. aPCC for the on-demand treatment of bleeding episodes.

Take home messages.

Results affected by treatment regimens and outcome assessment

○ The treatment regimen with rFVIIa associated with overall lower direct costs than the regimen with PCC [13].

○ In spite of the higher acquisition costs, greater initial efficacy of rFVIIa as first-line treatment (91–92% vs. 76.5–79% for aPCC) [13].

Setting: Cost analysis evaluations [13,21–25]; decision model approaches. Assumptions and treatment regimens [20,21] based on current country-specific literature data and/or expert opinion [13,23,24]. Incorporation into the lifetime model by Knight *et al.* [15].

Sequential use of rFVIIa and/or aPCC for bleeding management.

a. home treatment with rFVIIa or aPCC, evaluated as first stage;

b. rFVIIa (or aPCC) in hospital or at home,

c. rFVIIa only in hospital (when bleeding is not controlled)

First-line treatment with rFVIIa or aPCC at home or at the hemophilia Centre [21,22,25–27].

a. Costs due to high-dose FVIII, porcine FVIII or aPCC also included.

b. If bleeding persists after initial treatment, in-patients and/or out-patients will receive the same or a different agent.

○ aPCC less expensive than rFVIIa when patients' perception is evaluated 48 h after starting the treatment.

Setting FENOC study [29]: Cost-effectiveness evaluation, crossover study based on US, Swedish and Turkish drug acquisition costs; large individual variability in pain reduction after treatment; limited number of joint bleeds evaluated.

○ a single dose of rFVIIa 270 µg kg⁻¹ as safe and effective as rFVIIa 90 µg kg⁻¹ × 3 dosing and a more effective alternative to aPCC for the management of joint bleeding in patients with inhibitors.

Setting: Randomized comparison of home treatment of joint bleeds in a large cohort of haemophilia patients with inhibitors [30].

[] = reference[s] of the present report which to refer to for an in-depth analysis of the issue(s).

have used a decision model approach. Assumptions of the model and treatment regimens were the ones adopted by Odayemi and Guest [21,22]; they were incorporated into the lifetime model described by Knight *et al.* [15]. Briefly, these analyses take into account an initial and subsequent treatment for a bleeding episode; the probability of switching from one treatment regimen to another; the probability of success of each regimen and the risk of re-bleed with the subsequent treatment needed. In the frame of country-specific costs for concentrates and direct medical costs related to in-patient or out-patient hospital care, these studies have been recently reviewed [14] and classified into two major categories [13].

- Some studies have compared lifetime costs [13] or costs per resolved bleed [22,23] in different regimens, according to the sequential use of rFVIIa and/or aPCC for bleeding management. Three treatment stages have been considered: home treatment with rFVIIa or aPCC, evaluated as first stage; rFVIIa (or aPCC) in hospital or at home, and rFVIIa only in hospital (when bleed is not controlled) in the second and in the third stage, respectively. Assumptions for these models were driven from current Country-specific literature data and/or expert opinion [13,14,23,24].
- Other studies have evaluated the costs per resolved bleed using a first-line treatment with rFVIIa or aPCC at home or at the hemophilia Centre [21,22,25–27]. In some cases, costs due to high-dose FVIII, porcine FVIII or prothrombin complex concentrates have been also included. If bleeding persists after the initial treatment, in-patients as well as out-patients are considered to receive the same or a different agent. In these studies too, assumptions were derived from the literature and/or from country-specific data.
- As reported in detail in a recent review of these analyses [13,14], the treatment regimen with rFVIIa was predicted to be associated with overall lower direct costs for the management of mild/moderate bleeds, than the regimen with a PCC as first-line or first- and second-line treatment. In both cases, lifetime costs (~10% lower) [16] or costs per resolved bleed (13.5–39% lower) were taken into consideration [23,24]. In spite of the higher acquisition costs of rFVIIa, this agent was less expensive mainly because of its (assumed) greater initial efficacy as first-line treatment (91–92%) when compared to aPCC (76.5–79%) [13]. Accordingly, in spite of the wide variability in the reported cost reduction (from ~4% [26] to ~40% [21,26]), when total direct costs per resolved bleed

were evaluated rFVIIa appeared to be a less expensive first-line on-demand option [13,14].

- The latter analysis has been challenged. The use of assumptions based only on expert opinions, the lack of consideration of costs associated with re-bleeds, the risk of overestimation of rFVIIa doses and of underestimation of aPCC acquisition costs, are critical points in the study design [28]. The costs of the initial 24-h home treatment of a minor bleed of the shoulder in a US child were reported to be lower with aPCC than with rFVIIa (21 000 vs. 33 400 US\$). The cost-effectiveness evaluation of the crossover FENOC study, based on US, Swedish and Turkish drug acquisition costs indicated that aPCC was less expensive than rFVIIa when patients' perception of treatment efficacy was considered 48 h after starting the treatment. However, the large individual variability in pain reduction after treatment and the limited number of joint bleeds evaluated in the FENOC study (only one episode/patient per each agent) may affect the interpretation of the results of this analysis as well [29]. The report by Young *et al.* [30] supports this caution.
- In a randomized comparison, patients received a single dose of rFVIIa 270 $\mu\text{g kg}^{-1}$ or rFVIIa 90 $\mu\text{g kg}^{-1} \times 3$ (h 0, 3 and 6) or a single dose of 75 U kg^{-1} aPCC [30]. Efficacy was assessed by evaluating the need for additional haemostatic agents within 9 h. The percentage of rFVIIa 270 $\mu\text{g kg}^{-1}$ patients requiring additional haemostatic factors within 9 h was 4- to 5-fold lower than that for aPCC group (8.3% vs. 36.4% $P = 0.032$). Although comparable to that of the 270 $\mu\text{g kg}^{-1}$ group (8.3% vs. 9.1%), the percentage of rFVIIa 90 $\mu\text{g kg}^{-1} \times 3$ requiring such rescue medication (9.1%) did not reach statistical significance, when compared to aPCC group, ($P = 0.069$). As to secondary efficacy endpoints (pain and mobility) there was no difference within the three groups. Likewise no difference was seen as to safety in the three groups. Thus Young *et al.* [30] concluded that a single dose of rFVIIa 270 $\mu\text{g kg}^{-1}$ is as safe and effective as rFVIIa 90 $\mu\text{g kg}^{-1} \times 3$ dosing and appears to be a more effective alternative to aPCC for the management of joint bleeding in patients with inhibitors.

The lifetime evaluation of cost-effectiveness of different strategies of treatment of patients with high-responding inhibitors (Table 5)

- Costs of ITI. ITI is presently the only therapeutic approach to eradicate or reduce inhibitors, and

Table 5. The lifetime evaluation of cost-effectiveness of different strategies of treatment of patients with high-responding inhibitors.

Take home messages

1. Costs of ITI

~8-fold higher FVIII consumption and costs in patients with unfavorable prognosis (i.e. with time to 50% success of 19 months).

Setting: Extrapolation of data from the International Immune Tolerance Registry (IITR) [32].

Major determinants of ITI costs:

- a. the concentrate dose prescribed
- b. the patient body weight
- c. the duration of treatment (time to 50% success twice as long [19.0 vs. 9.5 months] in subjects with:
 1. inhibitor titer at ITI start >10 BU mL⁻¹;
 2. FVIII dose <100 IU kg⁻¹;
 3. interval from the inhibitor diagnosis and ITI >5 years).

2. 'Costly can be cheaper'

ITI vs. life-long on-demand treatment of bleeds: cost-effectiveness and cost-utility analyses [35].

- Annual ITI costs 15-fold higher than on-demand treatment.
- Annual ITI costs limited to 1–3 years, lifetime costs for on-demand treatments.
- Considerable long-term reduction of costs in the majority of treated patients.

Setting: Decision model based on expert consensus and published data. Estimates of on-demand vs. ITI year costs of treatment of a child (or an adult patient).

- Mean annual costs of on-demand treatment in an inhibitor patient 3-fold higher than in non-inhibitor patients.
- Mean ITI costs 3-fold higher in high-responder than in low-responder children. Higher differences in adults.

3. ITI vs. life-long on-demand treatment of bleeds: Lifetime perspective decision model analysis [15].

- Overall costs: On-demand (OD3) lifetime costs comparable to the Malmö ITI and lower than the Bonn ITI and the low-dose ITI protocol.
 - Cost-utility analysis: OD3 the worst QALY (25), best values for the Bonn ITI protocol (33.0); intermediate values for the Malmö ITI (28.1) and the low-dose ITI (29.1) protocols.
 - Incremental cost effective ratios (ICERs, cost per QALY): the Malmö ITI protocol as the most cost-useful, followed by the low-dose and then by the Bonn ITI protocol.
 - Clinical extrapolation: the low-dose ITI protocol as the best compromise as to cost-utility.
- Setting: Economic model focused on costs of treatment, including haemostatic agents, hospitalizations, orthopedic procedures, and expected lifetime clinical outcomes for patients with high-responding inhibitors. Mortality, arthropathy and quality of life are also included in the analysis. The success rate and the duration of three ITI protocols (Bonn, Malmö and low-dose, <100 IU kg⁻¹) is evaluated according to published data, with 10% high-responders becoming low-responders after ITI, and outcomes following ITI lasting for the patient's lifetime. Prophylaxis (30 IU kg⁻¹ three times a week) as the therapeutic choice following ITI success [15]. Costs of concentrates in the UK in 2001 used for the economic analyses.
- Lifetime evaluation in a boy from 2 years of age (13 kg) until 19 years of age (≈ 64 kg).
 - Regimens for on-demand treatment of bleeds:
 - aPCC as first-line option and rFVIIa or porcine FVIII as rescue.
 - Only rFVIIa in all stages of treatments (OD3).
 - Hospital admission in all cases of re-bleeds or major bleeds.

[] = reference[s] of the present report which to refer to for an in-depth analysis of the issue(s).

restore the standard FVIII treatment and prophylaxis feasibility, with its advantages in terms of safety and efficacy [7,8,31]. Because of the repeated, often high-dose, long-term concentrate administration, ITI is a highly demanding treatment for healthcare resources. On the other hand, in view of its effectiveness in about half of such patients, the lack of data allowing for the optimal selection of candidates and of modalities of treatment (timing, dosing, scheduling, type of concentrates) casts doubts on cost-effectiveness of ITI. Few studies have addressed the issue of costs of ITI, their impact in a lifetime perspective being evaluated only in few cases. Aledort *et al.* addressed the issue of costs of ITI by an extrapolation of data from the International Immune

Tolerance Registry (IITR) [32]. Major determinants of ITI costs were the concentrate dose prescribed, the patient body weight and the duration of treatment (time to success). The latter was significantly affected by the different patient prognostic factor profiles as detected in the IITR [33]: an unfavorable profile, was characterized by inhibitor titer at ITI start >10 BU mL⁻¹; FVIII dose <100 IU kg⁻¹, and an interval from the inhibitor diagnosis and ITI >5 years, the time to 50% success being twice as long (19.0 vs. 9.5 month) as that of subjects with favorable prognostic factors. This difference leads to about 8-fold higher FVIII consumption and costs (8 850 000 vs. 1 425 000 IU). Based on the drug acquisition prices at the time of the study, ITI with

plasma-derivative products was 50% cheaper than that with recombinant products [32].

- ITI vs. life-long on-demand treatment of bleeds: cost-effectiveness and cost-utility. In a decision model based on expert consensus and published data, Auerswald *et al.* [34] estimated on-demand vs. ITI year costs of treatment of a child (or an adult patient). Mean annual costs of on-demand treatment in an inhibitor patient resulted 3-fold higher than in non-inhibitor patients, both in children (27 857 vs. 76 511 €) and in adults (128 993 vs. 353 794 €). Mean ITI costs were about 3-fold higher in high-responder than in low-responder children (1 150 200 vs. 421 740 €). This difference was even higher in adults (5 751 000 vs. 575 100 €). As a whole, annual ITI costs were almost 15-fold higher than on-demand treatment in patients with inhibitors. However, this huge amount of costs is limited to 1–3 years, whereas costs for on-demand treatment last lifetime. Additionally, the high success rate and the low number of inhibitor recurrence after ITI, enables to restore standard FVIII strategy in a large amount of such subjects. As a consequence, a considerable reduction of costs in the majority of treated patients is achieved [35]. A US report [35] ('costly can be cheaper'), that estimated lifetime costs of treatment of a 5-year-old child with high-responding inhibitor undergoing ITI or only treated with aPCC on-demand, supported this notion. ITI was associated with an increase of life expectancy of 4.6 years and lower lifetime costs (about 1 700 000 US\$). However, the lack of rFVIIa cost analysis in this study and differences between US ITI protocols and clinical practice in other countries may affect, at least in part, the relevance of this report.
- Lifetime perspective decision model analysis. To quantify cost reductions with different treatment approaches, and to introduce the cost-utility approach with consideration of gain in terms of HRQoL, a complex decision model analysis has been proposed by Knight *et al.* [15,36]. This economic model is focused on costs of treatment, including haemostatic agents, hospitalizations, orthopedic procedures, and expected lifetime clinical outcomes for patients with high-responding inhibitors. Mortality, arthropathy and quality of life are also included in the analysis. The lifetime evaluation, based on a 3-month cycle length, takes into consideration a boy from 2 years of age (13 kg, according to the UK growth profile) until 19 years of age (≈ 64 kg). Three regimens are considered for on-demand treatment of bleeds that

employ aPCC as first-line option and rFVIIa or porcine FVIII as rescue (OD1 and OD2) or only rFVIIa in all three stages of treatment (OD3). In all cases of re-bleeds or major bleeds, hospital admission is assumed. The success rate and the duration of three ITI protocols (Bonn, Malmö and low-dose, <100 IU kg⁻¹) is evaluated according to published data, with 10% high-responders becoming low-responders after ITI, and outcomes following ITI lasting for the patient's lifetime. Prophylaxis (30 IU kg⁻¹ three times a week) is considered as the therapeutic choice following ITI success [15]. Costs of concentrates in the UK in 2001 are used for the economic analyses. As to overall costs, OD3 lifetime costs (2 047 000 £) are comparable to the Malmö (1 986 891 £) and lower than the Bonn (3 407 752 £) and the low-dose (2 374 650 £) ITI protocols. When cost-utility analysis is considered, the OD3 results are the worst QALY (25.1), whereas ITI is associated with better values. The Bonn protocol obtains the best value (33.0) in this setting, intermediate values being expressed by the Malmö (28.1) and the low-dose (29.1) protocols. On the whole, the comparison of incremental cost effective ratios (ICERs, cost per QALY) made the Malmö ITI protocol as the most cost-useful approach in a lifetime perspective, followed by the low-dose and then by the Bonn protocol. This advantage is mainly due to the shorter time to success, changes in the average duration of treatment and not in the success rate significantly affecting ICERs. However, as plasmapheresis and immunosuppressive agents are used in the Malmö protocol, this strategy does not reflect the common clinical practice of ITI. In view of these limitations, the low-dose ITI protocol appears to be the best compromise in terms of cost-utility and clinical extrapolation [15,36].

Pharmacoeconomic issues in haemophilia with inhibitors: limitations and unmet needs of the reports (Table 6)

- In the setting of haemophilia with inhibitors, a comprehensive analysis of the overall economic implications, together with a reliable evaluation in terms of morbidity, limb- or life-threatening bleeds, severity of arthropathy and its consequences in physical disability and psycho-social impairment, may only derive from long-term or lifetime perspective or observational studies. Presently (Table 2), most data for pharmacoeconomic analyses come from retrospective,

Table 6. Pharmacoeconomic issues in haemophilia with inhibitors: limitations and unmet needs of the reports.

Take home messages

- Cost-utility analysis (beneficial effects of a given treatment/healthcare intervention in terms of HRQoL), QALY (calculation of the net benefits of a cost-utility analysis), not analyzed in most studies

Setting: Most data for pharmacoeconomic analyses come from retrospective, short-term evaluations that only allow for the analysis of costs of concentrates and of other direct health costs. Comprehensive analysis of the overall economic and clinical implications, based on long-term or lifetime studies. ITI: since it may significantly affect the life expectancy of inhibitor patients, it allows for the use of the most cost-effective factor concentrate treatment of bleeds with major changes in the patient quality of life.

- Assumptions on clinical choices and outcome based on national or international clinical records, literature data or expert opinions, hamper the extrapolation, from country to country of specific cost analyses and decision-model approaches.

Setting: The reliability of these assumptions is the strength/limitation of these studies (differences in data sources; in medical practice and/or in healthcare systems and costs)

- The large variability of clinical choices (ITI vs. on-demand) in the management of inhibitor patients leads to dramatically different pharmacoeconomic evaluations.

Setting: As no general recommendation is presently possible, the scenario may dramatically differ with reference to the type of inhibitor population studied (children vs. adults, low-responding vs. high responding inhibitors); when to start; dose/type of product to use; alternative strategies (e.g. immunomodulatory approaches in patients in whom ITI fails).

short-term evaluations that only allow for the analysis of costs of concentrates and of other direct health costs [6].

- In the setting of chronic diseases, the cost-utility analysis that takes into account the beneficial effects of a given treatment/healthcare intervention in terms of HRQoL, is likely to be the most appropriate approach. To calculate its net benefits, the QALY, that significantly reflects such health gain has to be compared with its economic impact. Several current pharmacoeconomic studies are only based on a very limited healthcare payer perspective.
- Decision-model approaches that rely on assumptions as to clinical choices and outcomes are based on national or international clinical records, literature data, or expert opinions. The reliability of these assumptions is the strength/limitation of these studies: differences in data sources; in medical practice and/or in healthcare systems and costs, hamper the extrapolation, from one country to another of a specific cost analysis.
- As no general recommendation is presently possible in the ITI management of inhibitor patients, the large variability of clinical choices leads to very different pharmacoeconomic evaluations. This scenario is especially true when taking into consideration the type of inhibitor population studied: children vs. adults, low-responding vs. high responding inhibitors. In the studies reported above, his information is often unclear.
- Only prospective studies possess the strength for assessing the impact of therapeutic procedures that, in spite of their highest costs over a short period of time, are likely to reduce lifetime overall

costs. This is the case of ITI: since it may significantly affect the life expectancy of inhibitor patients, it allows for the use of the most cost-effective factor concentrate treatment of bleeds. For instance, thanks to ITI, orthopaedic surgery is presently carried out in these patients with major changes in their quality of life [6,13,15]. Most current pharmacoeconomic studies do not meet such needs.

- A series of clinical issues with respect to ITI regimens deserve to be addressed: when to start; dose and type of concentrate to use, strategies, including associated/alternative immunomodulatory approaches, for patients in whom ITI fails, etc. [29]. Among them, special emphasis should be put on FVIII dose and type of product. On-going studies are expected to provide significant information in this respect [37,38]. Although there are no conclusive data to support the superiority of any FVIII product in ITI [31], the Frankfurt ITI experience [39] and other recent studies [40–43] indicate a favourable role of VWF-containing FVIII products as to ITI outcome, in particular in patients at high-risk of poor response. Presently, as shown in the survey by the European Haemophilia Treatment Standardization Board [44], the concentrate used at inhibitor diagnosis is usually also chosen for ITI. Moreover, while in adults both plasma-derived and recombinant products are employed, in children recombinant products are the only current choice. In the on-going retrospective-prospective Italian ITI Registry (the PROFIT study), FVIII/VWF products were prescribed for 26/102 ITI courses, the majority of them being in subjects older than 20 years of age [45].

Perspectives (Table 7)

To extrapolate pharmacoeconomic data to clinical practice, one should take into account the wide variability of patient responsiveness, including treatment outcomes. Presently, the lack of general recommendations for the management of inhibitor patients makes it unlikely to define optimal treatment approaches as to specific clinical settings. Being designed to answer questions of resource allocation and effectiveness, decision models that use reliable data sources, including those from observational data, are the golden standard. To optimize the limited healthcare resources in most Countries, prospective and long-term studies in the setting of haemophilia with inhibitors are urgently needed for up-to-date cost-utility analyses and estimates of effectiveness. This task is rather complex to be faced in a different fashion. Few directions to be pursued are summarized below.

- In the frame of on-demand treatment of bleeding, the increasing use of high single rFVIIa dose or of combined by-passing agent approaches, may contribute to increase the efficacy and the cost-effectiveness of treatment. Together with the spreading of prophylactic approaches, these promising perspectives should be extensively studied [5,6];
- Beyond the well-recognized benefits on joint outcome and quality of life, the initial increase of costs of prophylaxis could be balanced by the reduction of inhibitor development and, in turn, by the highest amount of medical and economic resources needed for the management of this severe complication. Recent data suggest new potential benefits of early prophylaxis in severe haemophilic children. A protective effect against the development of inhibitors has been shown in a case-control Italian study, reporting a 70% reduction of inhibitor risk in children starting prophylaxis at a median age of

35 months [46]. Similar findings were shown in the larger European Concerted Action CANAL study: early regular prophylaxis (started at a median age of 20 months) was an independent negative predictor associated with a 60% lower risk of inhibitor development than on-demand treatment in that report [47];

- As stressed by the cost-utility data by Knight *et al.* [15,36], the identification of predictors of success and of time to success is a major direction to be pursued to optimize ITI success/costs ratio. Because of the burden of interventions for improvement of their safety, costs of plasma products have become higher over the last decades. To improve ITI outcome in patients with negative predictors of success, the potential cost-saving of plasma-derived products should be pursued, as the difference of costs with respect to recombinant products differs now from that reported in the economic analysis based on the IITR [32];
- Careful definitions of when to start a treatment; regimens (dose and type of product) to employ, and inhibitor population (children/adults, low-responding/high responding inhibitors) to study, are needed to allow for comparable analyses.
- The threshold incremental cost-effectiveness ratio (ICER), or lambda (λ), is thought to play a central role of in the methods and application of cost-effective analysis. This concept has been critically reviewed. The ability of this parameter to provide useful information for determining the efficiency of using available resources to support new health care programs have been challenged [48,49]. Examples of how 'the silence of the λ ' have fostered decisions leading to increased expenditures on health care programs and concerns about the sustainability of public funding for health care programs without any evidence of increases in total health gains have been provided [49]. Whether and the extent to what caution is needed in employing ICER in future analyses, needs urgent clarification.

Table 7. Pharmacoeconomic issues in haemophilia with inhibitor: Perspectives.

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- Decision models that use reliable data sources, including those from observational data, to answer questions of resource allocation and effectiveness (golden standard).
 - Long-term (life-long) studies, best if prospective, for up-to-date cost-utility analyses and estimates of effectiveness.
 - Urgent directions to be pursued:
 - Combined by-passing agent approaches.
 - Early prophylaxis in severe haemophilic children to prevent inhibitor development and improve QALY.
 - Identification of predictors of success and of time to success to optimize ITI success/costs ratio.
 - ITI outcome improvement in patients with negative predictors of success.
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