Economic analysis of not running tenders for recombinant Factor VIII procurement: a simplified analysis to estimate an otherwise unknown pharmacoeconomic index

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ABSTRACT

Background Two approaches to the procurement of recombinant Factor VIII products are used by health systems: (A) the most common approach where acquisition tenders are not carried out; (B) the approach tested in the UK in which procurement is based on tenders. The respective cost-effectiveness is not known.

Objective To estimate the incremental cost-effectiveness ratio (ICER) for the comparison A vs B.

Methods The analysis evaluated: (i) Factor VIII cost with/without tenders; (ii) inhibitor development caused by switching between products; (iii) clinical and economic consequences of inhibitors. Information on these items was obtained from a literature search. Because of the scarce evidence available on some items, our analysis considered the 'most favourable' scenario—that is, some extreme though reasonable assumptions were adopted that were intentionally biased towards improving the ICER of the no-tender option.

Results and discussion We estimated an ICER for A vs B of £486 409 (€657 139; £1=€1.351) per quality-adjusted life year (QALY). Since pharmacoeconomic thresholds are ~£30 000 per QALY, our results indicate that the cost-effectiveness of acquisition strategies that avoid tenders is prohibitive. Because of the simplified nature of our analysis, this estimate is preliminary.

Conclusions The 'true' ICER of A vs B remains unknown, but its value is likely to be even worse than the unfavourable ICER of £486 409 (€657 139) per QALY.

fewer than 150 days of exposure, switches were unavoidable, particularly in adult patients.

The major concern is whether these switches can increase the number of patients who develop inhibitors. The evidence on this issue is very limited. The problem is further complicated by the, possibly different, risk of inhibitor development between plasma-derived Factor VIII and recombinant Factor VIII^{2,3} and between different generations of recombinant Factor VIII.⁴

If one considers ongoing experimental studies in patients with haemophilia A (eg, the SIPPET Study), further information is likely to become available on the relative immunogenicity of recombinant and plasma-derived products, but not on the risk of inhibitor development related to switches.^{2,3} Hopefully, monitoring real-world practice, particularly in the UK, will be the source of some useful information.^{5,6}

As pointed out by Iorio *et al.*,³ to properly evaluate the risk of inhibitor development attributable to switching, a 'non-switching' control group would be needed in which patients are kept on the same product throughout their lives. In practice, such control groups are largely lacking. In the past, it was extremely rare, if not impossible, for an adult patient with haemophilia to have used the same product throughout his life; likewise, in the near future, no experimental study is likely to enrol a sufficiently large control group of patients kept on the same recombinant. Therefore, well-designed large-scale observational studies seem to be the only means to generate further knowledge on this complex issue.

The objective of this work was to conduct an economic analysis to estimate the incremental cost-effectiveness ratio (ICER) of not running tenders for Factor VIII procurement versus running these tenders. Our analysis therefore compared no tender versus tender, where the no-tender scenario is known to be the one most commonly practised in Western countries. The design of our analysis was to compare no-tender versus tender (and not the opposite way), simply because most pharmacoeconomic analyses are designed to compare the more costly option with the less costly one and not vice versa.

The main determinants influencing this ICER are recognised to be the unit cost of Factor VIII negotiated by the National Health Service (NHS) (in the presence or absence of a tender system) and both the clinical and economic consequences in terms of

INTRODUCTION

In the UK, nationwide experience over nearly a decade has focused on procurement of recombinant Factor VIII for use in patients with haemophilia A. This experience has been described in detail by Hay.¹ Briefly, implementation of nationwide tenders for purchasing recombinant Factor VIII has led to a substantial discount in the unit price of Factor VIII (an overall price discount of about 50% over a decade). The main disadvantage of this approach is that some patients are 'forced' to switch from one product to another because consumption must be selectively maximised in favour of the product that wins the tender.

In evaluating the pros and cons of the procurement strategies, the first question is whether the mandatory switches related to the results of the tender have any negative clinical consequences. Although the approach adopted in the UK has tried to avoid forced switches in paediatric patients with

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increased rate of inhibitor development. As pointed out above, an increase in inhibitor development is generally perceived to be related to the more common switches occurring when tenders are used, but sound evidence is lacking.

Reliable information on some of these determinants of clinical and economic outcomes is available from the literature. The following items are likely to be the most relevant: (a) unit cost of Factor VIII in the presence of tenders; (b) unit cost of Factor VIII in the absence of tenders. Less reliable but nevertheless acceptable literature information can be found on other determinants, particularly (c) the economic consequences of the development of new inhibitors. In contrast, data on other important clinical determinants are known to be very limited—for example, (d) increased rate, if any, of inhibitor development related to switching between different products; (e) lifetime impact of the development of new inhibitors on life expectancy and quality-adjusted life expectancy.

In the first phase of our study, we systematically reviewed the literature on these five items (a–e). In the second phase, we quantitatively combined the information obtained from this literature analysis to estimate the ICER of no-tender versus tender.

MATERIALS AND METHODS

Literature search and data extraction

Our literature search was exclusively based on the PubMed version of Medline (<http://www.pubmed.org>). The first extraction of articles was based on the following keywords: inhibitor* AND (hemophilia OR haemophilia) AND ('factor VIII' OR 'factor 8') combined with the filter 'Abstract available'. Two of us (AM and VF) read the abstracts of all articles selected through this search and identified the subset of articles that were potentially suitable for our analysis. After obtaining the full text of this subset of papers, we further selected those reporting information on items (a)–(e). The same article could be used for more than one item of our study. Finally, the selected articles were classified into the five groups (a–e) that represented the final material used for our analysis.

Pharmacoeconomic analysis

Pharmacoeconomic studies are typically carried out by determining a base-case scenario and by accompanying the base-case estimate of ICER with a series of sensitivity analyses (in which the key factors are varied over reasonable ranges to assess the effect of these changes on the ICER). We considered that the clinical and economic material available on this topic was insufficient to apply this typical approach of pharmacoeconomic analysis. Furthermore, the more unfavourable the consequences of inhibitor development are in both clinical and economic terms, the better the ICER is for the no-tendering strategy; for this reason, while keeping all of our parameter estimates within a reasonable range, we did not undertake any base-case analysis (with its related sensitivity analyses), but we directly estimated the ICER of the no-tender option for the worst clinical scenario. Since this worst clinical scenario corresponds to the most favourable ICER for the no-tender option, our rationale was as follows: if the estimates of this clinically worst ICER (intentionally biased towards a favourable pharmacoeconomic profile for the no-tender option) are unfavourable, this pharmacoeconomic result can easily be interpreted and is therefore informative in practical terms (ie, prohibitive cost-effectiveness for the no-tender strategy).

The ICER was estimated as the ratio of incremental cost divided by the gain in quality-adjusted life years (QALYs). No discounting was introduced in the various parameters.

RESULTS

Literature analysis

The extraction of articles from PubMed (last search run on 22 May 2015) yielded a total of 2443 citations. The full text was obtained for a subset of 86 papers which were divided into the five groups (a)–(e). Many of these articles were assigned to more than one group.

After reading these papers and extracting the pertinent information from selected papers, the various data were organised according to the following items: (1) economic consequences of developing high-titre inhibitors in haemophilia A; (2) annual cost of recombinant Factor VIII; (3) effect of Factor VIII switching on the development of inhibitors; (4) loss of quality-adjusted life expectancy resulting from inhibitor development. These four items are described in the following sections.

(1) Economic consequences of developing high-titre inhibitors in haemophilia A. Although numerous studies have addressed this issue,^{7–15} the current information on this point still shows some heterogeneity. The study by Bohn *et al*⁸ found a mean yearly cost per patient of US\$141 000 (€125 701; US\$1=€0.8915) for patients with inhibitors versus US\$80 000 (€71 320) for patients without inhibitors. Over the same period, Gringeri *et al*¹⁰ recorded a monthly cost of €18 000 (ie, about €215 000 yearly) in patients with inhibitors. The oldest of these studies¹² found an average yearly cost of \$C96 000 (€63 859; \$C1=€0.6652) compared with \$C43 000 (€28 604) without inhibitors. As pointed out by Di Minno *et al*,⁷ the wide variability in these cost estimates is intrinsically related to the clinical variability of the disease course in these patients.

In our view, the best economic estimate for the management of patients with inhibitors is represented by the most recent analysis in this area published by Valentino *et al*.¹³ These authors examined a large US sample including 981 patients without inhibitors and 63 with inhibitors and found a median annual overall cost of US\$63 935 (€56 998) with a median annual drug cost of US\$47 626 (€42 459) for patients without inhibitors and a median annual overall cost of US\$201 735 (€179 847) with a median annual drug cost of US\$191 301 (€170 545) for patients with inhibitors. According to these estimates, the presence of inhibitors implies a median increase in the annual cost per patient of about US\$138 000 (€123 027). To make a lifetime estimate of the economic consequences of inhibitor development, the estimate of the increase in annual cost should be extended over an appropriate period representing the duration of tolerance induction. According to the controlled trial by Hay & DiMichele,¹⁶ these interventions can have a duration of up to 33 months (ie, 2.75 years). Hence, if one multiplies the increase in annual cost (US\$138 000 (€123 027)) by 2.75, the resulting estimate (US\$ 380 000; €338 770) represents the median increase in lifetime cost per patient that can be attributed to the development of inhibitors. This figure is in keeping with the findings of Auerswald *et al*¹⁷ indicating an annual cost of €354 000. Furthermore, it has been observed that the median represents an underestimate of the true cost because outlier patients showing extremely high costs are not accounted for.¹³ On the other hand, Colowick *et al*¹⁴ reported that inhibitors can generate an increase in lifetime cost of about US\$1 million (€891 500).

Since our analysis aimed to test the worst scenario (from the perspective that: (i) tenders are used for Factor VIII acquisition; (ii) switches are thereby increased in their frequency; (iii) a putative increase in patients developing inhibitors is generated), in the context of our worst-scenario analysis we adopted the estimate of a cost increase of US\$1 million for every patient who

develops inhibitors. However, our impression is that using this figure produces an overestimate of the 'true' value. For example, the assumption that the cost increase has a duration of 33 months seems to be an overestimate when compared with the findings of Hay *et al.*¹⁶ where the mean duration of the intervention was about 15 months, and the simulation model described by Colowick *et al.*¹⁴ where this duration was set at 420 days.

(2) Annual cost of recombinant Factor VIII. The design of our pharmacoeconomic comparison focused on tendering versus not tendering. Since there was one article in the literature that specifically examined this issue,¹ that article was used as the main source of information needed for our analysis.

(3) The effect of Factor VIII switching on the development of inhibitors. As previously pointed out, reliable evidence is still lacking on this issue. Matino *et al.*¹⁸ addressed this question by undertaking a Delphi-panel study which involved 12 expert panellists. Interestingly enough, an agreement of 84% was recorded on the statement 'if several switches [...] are determined by a tender system, the [...] increase in the inhibitor incidence, if any, lies in the order of <3 to 5 in 1000 patient years. However, some evidence does exist on this issue, albeit quantitatively scarce and methodologically weak. Iorio *et al.*³ observed that 'the cumulative inhibitor risk in previously untreated patients (PUPs) is approximately 30%, whereas in polytransfused patients (PTPs) it is 2 to 3 per 1000 patient-years'; three references^{2, 19, 20} were offered in support of this statement. Finally, Santagostino *et al.*²¹ confirmed that there is no evidence to support the hypothesis that switching Factor VIII products can increase the risk of inhibitor development.

(4) Loss of quality-adjusted life expectancy resulting from inhibitor development. Data collected before 1993 showed that the presence of inhibitors in patients with haemophilia A results in a twofold increase in mortality compared with patients without inhibitors.²² However, these trends have not been confirmed. According to more recent studies,^{23–25} it seems that the life expectancy of patients with inhibitors (unadjusted for quality of life) does not differ from that of patients without inhibitors.²²

The issue of whether quality of life (expressed as utility) is worsened by the presence of inhibitors (and to what extent) has not been addressed by a sufficient number of studies. According to Gringeri *et al.*¹⁰ patients with severe haemophilia A show no differences in quality of life related to the presence or absence of inhibitors. In contrast, Knight *et al.*²³ found a loss in utility of 0.19, but no sound data were presented on how long this worsening of quality of life is likely to last.

For the purposes of our analysis, we assumed that the presence of inhibitors has an effect on the life expectancy of these patients. However, quantifying this loss in life expectancy is difficult. A crucial point is that information on life expectancy collected over the past century was negatively influenced by the effect of infection with HIV and/or HCV, the role of which—fortunately—is now negligible. The study by Tagliaferri *et al.*²⁵ has the merit of differentiating between recent patient series and the older ones. In addition, the mortality data have been corrected to account for the currently reduced effect of HIV and HCV on survival. According to the Tagliaferri study, life expectancy in 'recent' patients with haemophilia without inhibitors was essentially the same as that of the Italian male population (according to the 2005 national demographic survey²⁶). On the other hand, life expectancy of patients with haemophilia was found to be worsened by the presence of inhibitors: in particular, a multivariable regression analysis showed that inhibitors

imply a hazard ratio (HR) of 2.20 (95% CI 1.40 to 3.46) in relation to the end point of mortality.

To convert this HR into an estimate of the loss in life expectancy, we first plotted the life expectancy curve of the healthy Italian male population. Then, in the same graph, we added the predicted survival for patients with inhibitors that incorporated a HR of 2.20. Both curves are shown in figure 1. To estimate life expectancy from these two curves, we used the commonly used method of estimating their respective areas under the curve.²⁷ The results from these estimations indicated a (undiscounted) life expectancy of 78.33 years per patient for the reference curve and 70.10 years per patient for the population with haemophilia and inhibitors. This analysis therefore showed that the presence of inhibitors determines a loss in life expectancy of 8.23 years per patient. After incorporating the typical utility observed in haemophilia patients (utility 0.85 according to Knight *et al.*²³), the final estimate of this loss was 6.99 QALYs per patient.

Pharmacoeconomic analysis: calculating the ICER of not using tenders

The reference scenario adopted for our analysis (ie, estimation of the 'most favourable' ICER for the no-tender option) is described in tables 1 and 2. These tables summarise the various parameter estimates obtained from our literature analysis and used for the ICER calculation.

In this scenario, the ICER calculated for the comparison of the no-tender strategy with the tender strategy showed a prohibitive value of £486 409 (€657 139) per QALY gained. It should be recalled that our analysis was intentionally biased, in terms of cost-effectiveness ratio, in favour of the no-tender option. This prohibitive ICER of £486 409 per QALY (€657 139) gained was designed to be the 'most favourable' that one can expect for the no-tender strategy; so, the true (and unknown) cost-effectiveness of the no-tender option is likely to

Figure 1 Demographic prediction of life expectancy in Italian males (solid black line) and patients with haemophilia A with inhibitors (grey line). The upper curve was obtained directly from the official national demographic survey carried out in 2005 (report published in 2010; see ISTAT²⁶) and previously included in the study by Tagliaferri *et al.*²⁵ The lower curve was obtained from the upper one by applying an excess mortality quantified according to the HR of 2.20 estimated through Cox regression analysis by Tagliaferri *et al.*²⁵ in their sample of 347 patients with haemophilia A and 97 patients with haemophilia B.

Table 1 Clinical and economic impact of the development of new inhibitors

Impact	Literature-based estimate	Worst-scenario estimate	Source of the worst-scenario estimate
Lifetime increase in cost per patient*	US\$380 000 €354 000	US\$1 000 000	Colowick <i>et al</i> ¹⁴
Lifetime loss in life expectancy*	Unknown	8.23 LYs	Figure 1 of the present article
Utility loss*	None (according to Gringeri <i>et al</i> ¹⁰)	0.19 (from 0.85 to 0.66)	Knight <i>et al</i> ²³
Lifetime loss in quality-adjusted life expectancy per patient*	Unknown	6.99 QALYs	Estimated by multiplying lifetime loss in LY and utility†
Incremental number of patients developing inhibitors every 1000 patient years due to switches between recombinant products (vs a baseline risk in the absence of tenders)	N=0	N=2 to 3 N=up to 5	For N=0: Gouw <i>et al</i> ⁴ For N=2–3: Iorio <i>et al</i> ; ³ Wight and Paisley; ¹⁹ Kempton; ²⁰ Iorio <i>et al</i> ² For N=up to 5: Martino <i>et al</i> ¹⁸

*Resulting from inhibitor development.

†Utility is assumed to be 0.85 to reflect the transition from absence to presence of inhibitors.

‡Gouw *et al*⁴ found some risk factors for inhibitor development, but not switching.

LY, life year; QALY, quality-adjusted life year.

be even worse than this unfavourable ICER of £486 409 (€657 139) per QALY gained.

DISCUSSION

Our study deals mainly with economic issues, but the primary driver of our analysis lies on the clinical side. As in many other analyses conducted in this area, studying the clinical determinants of a cost-effectiveness question is an essential prerequisite to identifying the best solutions to the problem. In fact, the present analysis was largely focused on clinical evidence. On the other hand, economic sustainability is a crucial factor in managing patients with inhibitors and so clinical and economic factors are strictly inter-related.

One important point is that the data presented in our analysis are from the perspective of a hospital (and, in more detail, from the perspective of a regional hospital network as is the case in Italy). When Factor VIII is instead prescribed in the public area, running tenders is much more difficult and, in many cases, impossible because of regulatory and administrative constraints.

From a methodological point of view, the empirical nature of our analysis is certain. However, one should keep in mind that, at the present state of knowledge (which is insufficient in general terms), decisions on this question still need to be made; in the absence of methodologically robust and exhaustive findings, empirical information can also be useful. One limitation of

our analysis is that only the results of the tenders conducted in the UK were considered. However, a recent survey on Factor VIII procurement methods conducted in 38 European countries²⁸ shows that tendering systems are quite widely adopted throughout Europe, and so the results of our analysis should be applicable in different countries.

Needless to say, the intent of our study was mainly provocative. Since in most countries the option of running tenders continues to be avoided, exploring the cost-effectiveness of the absence of tenders was worthwhile, at least for the purpose of stimulating a debate on this issue.

The recommendation from our results is that tenders are appropriate from a pharmacoeconomic point of view, whereas avoiding tenders seems to have a prohibitively unfavourable cost-effectiveness ratio. While this result is strictly dependent on the assumption that tenders result in a 20% discount in Factor VIII unit price, this assumption seems to be realistic and even conservative, because a 50% discount was obtained in the UK experience.¹

In other areas of pharmacotherapy, a large number of approved treatments, particularly in oncology, fail to represent value for money and, in fact, their ICERs exceed the commonly used values of threshold.^{29–30} However, the case with Factor VIII described in this paper differs because the ICER calculated from our analysis was many times higher than common thresholds. However, contrasting the ICER of Factor VIII procurement

Table 2 Estimates of cost and effectiveness normalised to a population of 1000 patients with haemophilia A without inhibitors

	Without tenders	With tenders	Reference
Annual cost of recombinant Factor VIII	£100 million (€135 million)	£80 million (€108 million) (assuming a 20% discount in prices*)	Hay ¹
Incremental number of patients developing inhibitors due to switches between recombinant products (vs a baseline risk in the absence of tenders)	–	N=5	Martino <i>et al</i> ¹⁸
Medical excess cost for every new patient developing inhibitors	US\$1 million (see table 1)	empirically converted into £600 000 (€811 000)	
Medical excess cost for N patients developing inhibitors	£0	£600 000×5=£3 million (€4.05 million)	See the previous row of the present table
Overall loss in quality-adjusted life expectancy for N patients with new inhibitors	0 QALYs	6.99×N=6.99×5=34.95 QALYs	See table 1

Calculation of the cost-effectiveness ratio: ICER for no-tender vs tender strategies=(increase in cost)/(QALYs gained)=£(20–3) million/34.95 QALYs=£486 409 per QALY gained.

*Hay¹ reported unit price reductions of 5% for the first national contract (2004–2006), 25% for the second national contract (2007–2010), and about 30% for the third national contract (2010–2014).

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

with unfavourable values of cost-effectiveness in other areas of pharmacotherapy was beyond the purpose of our study.

In conclusion, we emphasise that this paper should not be taken as a rigorous pharmacoeconomic study, but read more as food for thought in a controversial area.

What this paper adds

What is already known on this subject

- The majority of European countries do not use competitive tendering for Factor VIII procurement, but the decision not to use this strategy is generally made on an empirical basis.
- In comparing strategies of tendering versus not tendering, factors influencing the cost-effectiveness ratio of these two alternatives are well known (drug cost, risk of inhibitors), but no specific pharmacoeconomic analysis has been reported.

What this study adds

- Based on literature information on cost and effectiveness, we estimated the incremental cost-effectiveness ratio for the comparison of tender versus no tender.
- Our results indicate that the cost-effectiveness of procurement strategies that avoid tendering is prohibitive.

Contributors Guarantor of article: AM. All authors participated in the design of the study. AM, DM and ST carried out the literature search and the data extraction phase. AM wrote the first draft. VF and ST performed the economic analysis.

Competing interests None declared.

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