High-titre inhibitors in previously untreated patients with severe haemophilia A receiving recombinant or plasma-derived factor VIII: a budget-impact analysis

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Introduction

The SIPPET (Survey of Inhibitors in Plasma-Products Exposed Toddlers) trial[1] provided evidence that, in previously untreated patients with severe haemophilia A, recombinant factor VIII increases the risk of developing high-titre inhibitors as compared with plasma-derived factor VIII. This multicentre, international study enrolled 264 previously untreated patients (mean age, around 20 months) who were randomised to receive either recombinant factor VIII or plasma-derived factor VIII. Inhibitors developed in 29/125 patients treated with plasma-derived factor VIII (high-titre inhibitors: 20 patients) and in 47/126 patients treated with recombinant factor VIII (high-titre inhibitors: 30 patients). The cumulative rates of all inhibitors were 26.8% with plasma-derived factor VIII (high-titre inhibitors: 18.6%; 95% confidence interval [CI]: 11.2 to 26.0) and 44.5% with recombinant factor VIII (high-titre inhibitors: 28.4%; 95% CI: 19.6 to 37.2). This implies that, in the SIPPET trial, the relative risk reduction for the incidence of high-titre inhibitors was 34.5% for plasma-derived factor VIII compared with recombinant products. All inhibitors occurred before 39 exposure days; all high-titre inhibitors occurred before 34 exposure days (median: 7 to 8 exposure days).

These findings have important clinical implications, but their budget impact also deserves to be considered, particularly because of the high cost incurred in the treatment of high-titre inhibitors. In November 2015, we published a preliminary assessment on this topic based on the initial results of SIPPET and on a simple narrative analysis[2].

To address this issue better, in the present study we developed a Markov model and studied the economic consequences in terms of budget impact that, in previously untreated patients with severe haemophilia A, can derive from using plasma-derived products as opposed to recombinant factor VIII.

Materials and methods

Our analysis employed a Markov model based on the results of the SIPPET randomised trial and on clinical and economic information previously reported in the literature. Our study was designed as a budget-impact analysis comparing previously untreated patients managed with plasma-derived factor VIII with those managed with recombinant factor VIII. The simulation model was developed using commercial software (TreeagePro, 2011 version; Treeage Software Inc., Williamstown, MA, USA). The main characteristics of the model are presented in Figure 1.

Our analysis was from the payer's perspective and excluded indirect costs. All costs are expressed in euros. Economic data expressed in American dollars were converted into Euro according to an exchange rate of € 1 = US$ 1.12.

Briefly, the core of our model is a decision node (not shown in Figure 1) from which two branches originate, the first describing the patients assigned to recombinant factor VIII (panel A in Figure 1) and the second those assigned to plasma-derived factor VIII (panel B in Figure 1). A total of ten states of health were included in the Markov model (see our online supplementary material for details).

In each of the two main sections of the model (i.e. recombinant factor VIII [panel A] and plasma-derived factor VIII [panel B]), the Markov analysis incorporated the adjustment for annual discount rates and traced the number of cycles evaluated in the iterative process.

The transition probabilities that manage how patients move across the health states are presented in panels A and B (Figure 1). Probabilities with values of 0 or 1 are self-explanatory; the symbol "#" identifies a probability equal to the value needed to reach 100% after taking into account the other probability/probabilities expressed in numerical form and assigned to the other branch(es) of the same node.

According to the Markov approach, costs incurred in the model are iteratively summed upon each cycle. Three items participated in the cost analysis, namely the annual cost per patient treated with recombinant factor VIII (denoted as "annual_cost_ric"), the annual cost per patient treated with plasma-derived factor VIII

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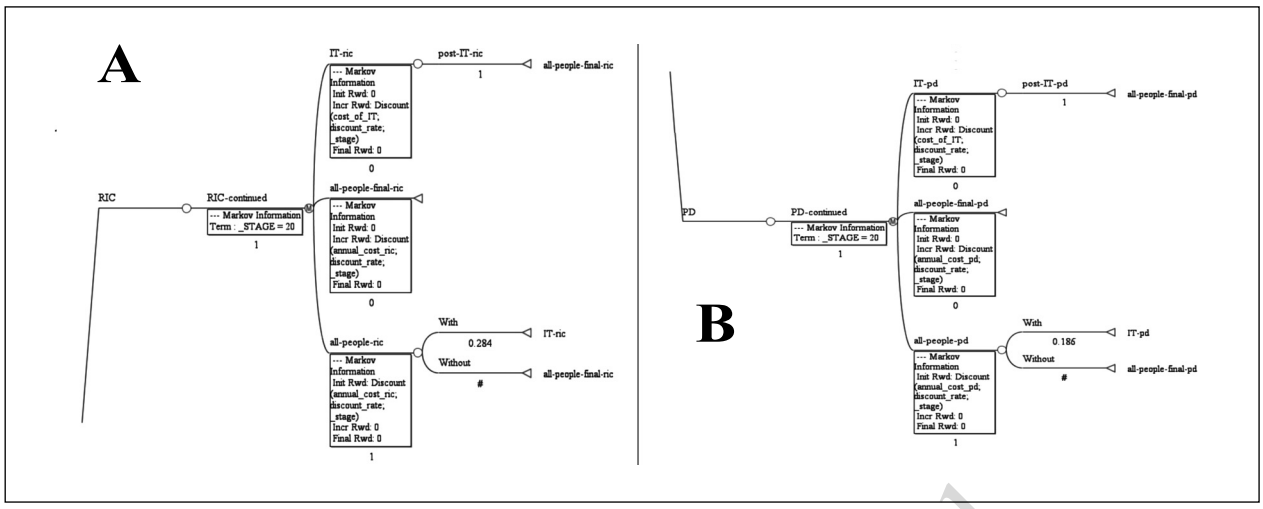

Figure 1 - States of the Markov model and transition probabilities.
The starting point of the simulation model is a decision node (not shown in this figure) from which two branches originate, the first of which describing the patients assigned to recombinant factor VIII (panel A) and the second the patients assigned to plasma-derived factor VIII (panel B). The symbols adopted in this scheme reflect the syntax required by the Treeage software (Ⓜ Markov node; O: probabilistic node ; ◁ terminal node).
RIC: recombinant; PD: plasma-derived; IT: immune tolerance; _STAGE: yearly cycle in Markovian simulations; RWD: reward (i.e. the variable expressing the cumulative cost).

(denoted as "annual_cost_pd"), and the cost per patient of immunotolerance therapy (denoted as "cost_of_IT"). As regards the syntax of the Treeage software, cost data were handled as "incremental rewards" (denoted as "Incr Rwd"). In other words, the variable "Rewards" was used to cumulate the various cost data at each cycle.

The variables included in our model reflect the main determinants likely to influence our budget-impact analysis. In the base-case analysis, all cost data were discounted at 3% yearly; the time horizon was set at 15 years.

In modelling the pattern of costs associated with the two types of factor VIII replacement therapy, the following variables were assumed to differ between the two cohorts of patients: (i) cumulative incidence of high-titre inhibitors (data obtained from the results of SIPPET); (ii) cost of treatment using plasma-derived or recombinant factor VIII products (data obtained from literature). Other variables were assumed to be the same for the cohorts (e.g. induction of immune tolerance and respective costs; time horizon; discount rate). Table I presents the values that, in our base-case analysis, were assigned to the main parameters of the model, along with the sources of these pieces of information. A series of one-way sensitivity analyses was performed to assess how the variations of the main model parameters influenced the economic results of our analysis (Table II).

Finally, it should be noted that the age and the average body weight of toddlers included in the SIPPET trial were lower than the typical values found in adult patients with haemophilia. It is well known that the cost

Table I - Model parameters employed in our base-case analysis*.

Item	Model parameter	Value	References
#1	Cost for each patient developing high-titre inhibitors	€ 891,500*	Maratea *et al.* 2016[3] Colowick *et al.* 2000[4]
#2	Annual cost per patient of treatment with recombinant factor VIII	€ 50,000	Based on expert opinion†
#3	Annual cost per patient of treatment with plasma-derived factor VIII expressed as percent reduction in comparison with the cost of using recombinant factor VIII	−20%	Based on expert opinion†
#4	Time horizon (years)	15	Based on expert opinion†
#5	Annual discount rate	3%	Abrahamyan *et al.* 2014[5]
#6	Increased incidence of high-titre inhibitors with recombinant factor VIII compared with plasma-derived factor VIII	9.8%**	Peyvandi *et al.* 2016[1]

*Cost values expressed in US$ were converted into € according to an exchange rate of 1 € = 1.12 US$; **Calculated from 28.4% with recombinant factor VIII *vs* 18.6% with plasma-derived factor VIII; †These values were decided by consensus among FP, RP, FRR, and PMM in the absence of any explicit reference, but taking into account the published literature.

Table II - Sensitivity analysis: model parameters incorporated in the Markovian simulations and results of the simulation study.

Analysis	Model parameter		Values of the model parameter	Model-predicted cost per patient managed with recombinant factor VIII (€)	Model-predicted cost per patient managed with plasma-derived factor VIII (€)	Model-predicted increase in the cost per patient (€)	References in support of the model-parameter value
#1	Cost for each patient developing high-titre inhibitors	Lower limit	€ 338,770§	694,425	545,505	148,920	Maratea *et al.* 2016[3]
		Upper limit	€ 1,200,000	931,891	700,192	231,699	Based on expert opinion†
#2	Annual cost per patient of treatment with recombinant factor VIII	Estimate N. 1	€ 30,000	649,079	450,919	198,160	Based on expert opinion†
		Estimate N. 2	€ 50,476§	894,193	649,386	244,807	Abraha-myan *et al.* 2014[5]
		Estimate N. 3	€ 135,000§§	1,906,016	1,468,702	437,314	Hay 2013[6]
		Estimate N. 4	€ 125,701§	1,794,699	1,378,567	416,132	Abraha-myan *et al.* 2014[5]
		Estimate N. 5	€ 156,904§	2,168,225	1,681,018	487,207	Abraha-myan *et al.* 2014[5]
		Estimate N. 6	€ 183,673§	2,488,672	1,940,492	548,180	Elder-Lissai *et al.* 2014[7]
#3	Annual cost per patient of treatment with plasma-derived factor VIII expressed as percent reduction in comparison with the cost using recombinant factor VIII	Estimate N. 1	0%	888,495	765,947	122,548	Based on expert opinion†
		Estimate N. 2	−33%	888,495	566,025	322,470	Mannucci *et al.* 2012[8]
		Estimate N. 3	−43%	888,495	505,443	383,052	Eandi *et al.* 2013[9]
		Estimate N. 4	−50%	888,495	463,035	425,460	Mannucci *et al.* 2012[8]
#4	Time horizon (years)	Lower limits	5	467,880	341,623	126,257	Based on expert opinion†
			10	671,331	504,383	166,948	Based on expert opinion†
		Upper limit	20	998,215	765,891	232,324	Based on expert opinion†
#5	Annual discount rate	Lower limit	0%	988,986	757,527	231,459	Abraha-myan *et al.* 2014[5]
		Upper limit	5%	772,538	585,972	186,566	Abraha-myan *et al.* 2014[5]
#6	Increased incidence of high-titre inhibitors with recombinant factor VIII compared with plasma-derived factor VIII	Lower limit	+5%*	806,796	644,782	162,014	Based on expert opinion†
		Upper limit	+15%**	888,495	644,782	243,713	Based on expert opinion†

§Cost values expressed in US$ were converted into € according to an exchange rate of 1 € = 1.12 US$; §§ Cost values expressed in sterling pounds (£) were converted into € according to an exchange rate of 1 € = 0.7402 £; *estimated by assuming an incidence of 23.5% *vs* 18.5% for recombinant factor VIII and plasma-derived factor VIII, respectively; **Estimated by assuming an incidence of 33.5% *vs* 18.5% for recombinant factor VIII and plasma-derived factor VIII, respectively; † These values were decided by consensus among FP, RP, FRR, and PMM in the absence of any explicit reference, but taking into account the published literature.

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of treatment with factor VIII is very strongly dependent on age and weight, as factor VIII requires weight-based dosing. However, given the budget-impact nature of our analysis, we did not introduce any sensitivity analysis focused on age and/or body weight because we chose to directly vary the annual cost of the replacement therapy (which is a direct consequence of the dosage adopted); a wide range of variation in this annual cost was therefore evaluated because the goal of our sensitivity analysis on this variable was also to test the effect of age and weight.

The presentation of our analysis is in line with most of the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) described by Husereau and co-workers[10].

Results

Our base-case analysis (time horizon: 15 years) estimated an average cost per patient of € 846,829 for the recombinant factor VIII cohort and of € 644,782 for the plasma-derived factor VIII cohort. The difference between these two treatment options was € 202,047 per patient over 15 years.

The results of our one-way sensitivity analyses are presented in Table II (columns 1 to 6). In testing the hypothesis of no difference in cost per international unit (IU) between the two types of factor VIII, analysis #3 (estimate N. 1) found a cost increase of about € 120,000 per patient over 15 years, which is lower than the value of about € 200,000 found in our base-case analysis. This indicates that this latter value of cost increase is due to a remarkable extent (~60%) to the higher cost per unit of recombinant factor VIII and to a lesser extent (~40%) to the consequences of the increased incidence of high-titre inhibitors with recombinant products. Accordingly, testing the variations from +5% to +15% for the increased incidence of high-titre inhibitors with recombinant factor VIII (analysis #6) showed a modest effect on the cost increase per patient between the two types of factor VIII, because this increase ranged from € 162,000 to € 243,000 (in comparison with € 202,000 of the base-case analysis). Varying the cost of immune-tolerance therapy from € 338,700 to € 1,200,00 (analysis #1) resulted into estimates of cost increase ranging from € 149,000 to € 232,000. On the other hand, the highest value of the increase in the cost per patient (€ 548,180) was associated with the assumption (analysis #2, estimate N. 6) that the annual cost per patient treated with recombinant factor VIII was € 183,673 (as compared with the assumption of € 50,000 adopted in the base-case analysis). In analysis #2, it is noteworthy that the hypothesis of a reduced annual cost of recombinant factor VIII (€ 30,000; estimate N. 1) was associated with a cost increase of € 198,160, which remains close to the base-case result; this hypothesis in part reflects the reduced dosage administered to toddlers, with a consequent reduction in annual cost.

Finally, analyses #4 and #5 (focused on variations in time horizon and discount rate) indicated that these two parameters had no important effect on the overall results.

Discussion

In the light of the results of SIPPET trial, the present study addressed an issue for which no specific data were available, but numerous questions are open. If recombinant products of factor VIII generate an increased incidence of inhibitors, are there any budget implications? To what extent is the overall cost per patient increased using recombinant products as opposed to plasma-derived ones?

The present analysis has expanded previous preliminary research conducted on this issue[2] and has one important advantage in that a specific simulation model was developed and applied to generate the pharmacoeconomic results. In our previous narrative analysis, we observed that, in the comparison between recombinant and plasma-derived factor VIII, the number needed to harm (NNH) was around 10 according to the results of SIPPET. In estimating the NNH (as well as the number needed to treat), results are known to be less biased if the analysis is based on the relative risk reduction (−34.5%) as opposed to the absolute risk reduction. If one applies a relative risk reduction of −34.5% to the incidence of 28.4% observed for recombinant products in SIPPET, the absolute risk difference (around −10%) yields a NNH around 10, as pointed out above. However, if one applies the relative risk reduction of −34.5% to other incidences of high-titre inhibitor development in patients given recombinant products (e.g. the incidences of 17.6 and 22.4% reported by Di Minno and co-workers[11]), the absolute risk differences are around −6.1 and −7.7%, respectively, and the corresponding values of NNH are 16.5 and 12.9, respectively. Hence, assuming an absolute risk difference around −6% and a NNH around 17 identifies a reduced monetary advantage which is approximately the value (increase of € 162,014 in the cost per patient) estimated in our sensitivity analysis #6 for an absolute risk difference of −5%.

From an economic viewpoint, this means that the use of recombinant factor VIII is associated with an average increase in the treatment cost per patient equal to the average cost of treating one case of high-titre inhibitors divided by 10. This in turn raises the need to estimate the average cost to treat one patient who develops high-titre inhibitors, which we conservatively assumed to be € 338,770 (even though estimates as high as € 800,000 have been reported in the literature). Dividing the above

(i.e. € 338,770) by 10 yields € 33,877 per patient. Hence, we conservatively concluded that the increase in cost was at least € 33,877 per patient if recombinant factor VIII is used instead of plasma-derived factor VIII.

The analysis described herein had a more complete design, assumed a longer time horizon, incorporated a rather large number of relevant variables and, most importantly, addressed these economic questions using a well-recognised instrument of data simulation. The results of our analysis estimated a much higher increase in per-patient cost (i.e. around € 200,000) if recombinant factor VIII is used instead of plasma-derived factor VIII.

Our study has limitations. First of all, despite its apparent complexity, our simulation model was a simplified one and only accounted for the main determinants influencing cost, whereas other variables were not considered (e.g. the timing expressed as exposure days at which inhibitors could develop). Some variables were not introduced in the model. For example, immune tolerance induction is usually performed in Europe using the same factor being given to the patient when the inhibitor developed[12]. Our model did not account for this criterion of factor VIII selection, but the wide range of expenditures for immune tolerance induction tested in our sensitivity analysis was likely to compensate for this lack of modelling.

Our model did not directly address the issue of the cost per unit of factor VIII, and so an in-depth discussion of this point is worthwhile. In the base-case analysis, our model incorporated a cost per unit of recombinant factor VIII of € 0.65[6,9]; this corresponds to a yearly amount of factor VIII per patient of around 46,000 IU. In the sensitivity analysis, this amount per patient per year was subjected to numerous upward variations and reached a maximum of more than 282,000 IU (Table II, analysis #2). Under the assumption of 100 or 150 administrations per patient per year, each administration consisted, on average, of 461 IU and 308 IU, respectively. Finally, since the time horizon of the analysis covered a total of 20 years and consequently the body weight of the simulated patients increased over this period, it should be stressed that numerous model-predicted parameters (including those presented above) represent an average in a context in which important variations are determined by the increase over time in the patients' body weight.

Another limitation of our study is that the range of values over which variations were assumed in the sensitivity analyses were sometime not based on specific information published in the literature, but rather reflected some assumptions made by consulting the co-authors of SIPPET, experienced in the treatment of haemophilia. Although the lack of some data in explicit form is, of course, a drawback to our study, it should be noted that this approach is frequent when a deterministic sensitivity analysis is undertaken.

We did not employ a lifetime horizon because predicting which treatments will be the standard of care for so many years (including replacement therapies and immuno-tolerance), and also predicting their future costs, would have increased the degree of uncertainty of our analysis. Likewise, we did not adjust the model based on the patients' life expectancy because this adjustment has a negligible impact, particularly if the time horizon is restricted to 15 years[3].

Another limitation is that, because patients included in the SIPPET trial were generally toddlers, assumptions about their body weight and the daily units of replacement factor VIII were difficult. This limitation was addressed by extending to six the values of annual cost of replacement factor VIII tested in sensitivity analyses.

Conclusions

The clinical implications raised by the randomised SIPPET trial on the choice of the less immunogenic source of factor VIII obviously remain the main focus, even in the framework of the present economic study. However, analysing the economic aspects, the use of recombinant factor VIII as opposed to plasma-derived products implies a relevant increase in the expenditure per patient (about € 200,000 over 15 years). This increased expenditure directly reflects the increased cost of recombinant products, in comparison with plasma-derived ones, and the economic consequences of the expected increase in the incidence of inhibitors in previously untreated patients with severe haemophilia A.

Finally, while in recent years innovative recombinant factor VIII products have been developed (e.g. enhanced half-life factor VIII products and factor VIII mimetics), the present analysis applies only to "traditional" plasma-derived or recombinant factor VIII products and not to the above-mentioned innovations.

Supplementary material

This material can be downloaded from http://www.osservatorioinnovazione.net/papers/bt-supplementary-material.doc.

Authorship contributions

AM, ST, FP, FRR, and PMM designed the study, analysed the results, and wrote the manuscript. AM developed the simulation model. ST, FP, RP, and FRR retrieved the literature included in the model. AM and ST collected the data. FP assisted with data analysis. The work of AM and ST was performed as part of their employment; PMM, FP, RP, and FRR, who work at their respective universities, carried out this study as part of their research in the field of haemophilia.

Keywords: factor VIII; inhibitor; pharmacoeconomics; Markov, chain.

Disclosure of conflicts of interest

AM, ST, RP, and FRR have no competing interests. FP reports grant support by the "Angelo Bianchi Bonomi" Foundation and the Italian Ministry of Health during the conduction of the study; grant support by Alexion; grant support and personal fees by Biotech, Novo Nordisk, and Grifols, and personal fees by Ablynx, Octapharma, Sobi, CSL Behring, Bayer, LBF, and Kedrion outside the submitted work. PMM has acted as a consultant for Bayer and Kedrion Biopharma and has received speaker fees by Baxter, Bayer, Grifols, Kedrion Biopharma, Novo Nordisk and LFB.

References

1) Peyvandi F, Mannucci PM, Garagiola I, et al. Randomized trial of factor VIII and neutralizing antibodies in hemophilia A. N Engl J Med 2016; **374**: 2054-64.
2) Messori A, Trippoli S, Marinai C. The SIPPET trial and the economic consequences of developing high-titre inhibitors in hemophilia A (Rapid Response). bmj.com, published on 17 November 2015. Available at: http://www.bmj.com/content/350/bmj.h870/rapid-responses. Accessed on: 25/03/2017.
3) Maratea D, Fadda V, Trippoli S, Messori A. Economic analysis of not undertaking tenders for recombinant factor VIII procurement: a simplified analysis to estimate an otherwise unknown pharmacoeconomic index. Eur J Hosp Pharm 2016; **23**: 219-23.
4) Colowick AB, Bohn RL, Avorn J, Ewenstein BM. Immune tolerance induction in hemophilia patients with inhibitors: costly can be cheaper. Blood 2000; **96**: 1698-702.
5) Abrahamyan L, Willan AR, Beyene J, et al; Canadian Hemophilia Primary Prophylaxis (CHPS) Study Group. Using value-of-information methods when the disease is rare and the treatment is expensive--the example of hemophilia A. J Gen Intern Med 2014; **29** (Suppl 3): S767-73.
6) Hay CR. Purchasing factor concentrates in the 21st century through competitive tendering. Haemophilia 2013; **19**: 660-7.
7) Elder-Lissai A, Hou Q, Krishnan S. The Changing Costs of Caring for Hemophilia Patients in the U.S.: Insurers' and Patients' Perspectives. Presented at: American Society of Hematology Annual Meeting; December 6-9, 2014; San Francisco, CA. Abstract #199.
8) Mannucci PM, Mancuso ME, Santagostino E. How we choose factor VIII to treat hemophilia. Blood 2012; **119**: 4108-14.
9) Eandi M, Pradelli L, Povero M. Costs of treatment of haemophilia A in Italy: comparison of the use of plasma-derived and recombinant factor VIII using a discrete event simulation (DES) model. Farmeconomia 2013; **14**: 51-74.
10) Husereau D, Drummond M, Petrou S, et el. ISPOR Health Economic Evaluation Publication Guidelines-CHEERS Good Reporting Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health 2013; **16**: 231-50.
11) Di Minno MN, Marchesini E, Valdrè L. Risk of inhibitors in previously untreated patients with hemophilia: a meta-analysis of literature studies. Blood 2015; **125**: 3819-21.
12) Gringeri A, Mantovani LG, Scalone L, Mannucci PM; COCIS Study Group. Cost of care and quality of life for patients with hemophilia complicated by inhibitors: the COCIS Study Group. Blood 2003; **102**: 2358-63.

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