Original article

FAR-BENE Study: pharmacoeconomics and well-being in hemophilia. Monitoring outcomes in light of pharmaceutical expenditure with focus on patients undergoing therapeutic switch

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Background - Hemophilia, a rare bleeding disorder, raises significant pharmacoeconomic challenges, particularly with the emergence of innovative therapies. This study evaluates clinical and patient-reported outcomes and expenditures in hemophilia patients focusing on those who underwent therapeutic switches between 2017 and 2023.

Materials and methods - This retrospective study included severe hemophilia patients. Expenditure was analyzed based on clotting factor consumption, while clinical well-being was assessed using ABR, NRS for pain, joint health scores (HJHS, HEAD-US) and trough plasma levels. A sub-analysis was conducted by applying different therapeutic groups. Statistical significance of differences between paired measures (pre [T0] *vs* post [T1]) was examined using the Wilcoxon Sum Rank test.

Results - Seventy patients were included. Total expenditure was € 12,947,580.44 in 2017 and € 12,967,576.92 in 2023. Among 45 patients who switched therapy, the median number of infusions/year significantly decreased from 156 to 91 ($p<0.001$), ABR from 1 to 0 ($p<0.001$) and NRS from 3,5 to 0 ($p<0.001$). Joint health did not show improvement with a slight but not statistically significant increase (HJHS from 10 to 15; HEAD-US from 7 to 8). Median trough increased from 3 IU/mL to 5 IU/mL ($p=0.181$). Patients were grouped for analysis based on homogeneous treatment regimens.

Discussion - This study is the first effort to conduct comprehensive analysis of the impact of therapeutic choices on well-being and cost of care in hemophilia Center. The study underscores the need for a value-based approach to hemophilia care, integrating expenditure and clinical outcomes. Adopting validated economic weight outcome in future pharmacoeconomic evaluations will be essential for decision making.

Keywords: *hemophilia, cost-effectiveness analysis, health expenditure, patient reported outcomes measures, treatment outcome.*

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INTRODUCTION

Pharmacoeconomics and sustainability of care are becoming increasingly important for clinicians and decision-makers, particularly in rare and chronic diseases where treatment is costly and continually evolving. Hemophilia A (HA) and B (HB) are rare X-linked bleeding disorders caused by a deficiency in clotting factor VIII (FVIII) or factor IX (FIX)[1] with a prevalence in the Italian population of about 1.36/10.000 and 0.29/10.000, respectively[2]. Treatment aims to prevent life-threatening bleeding and disabling comorbidities, particularly arthropathy caused by repeated hemarthroses and thereby to improve quality of life[3]. Prophylaxis is the most commonly chosen therapeutic regimen, especially for patients with severe hemophilia (FVIII/FIX, <1%), to obtain trough plasma levels of at least 1-2 IU/mL[4-6]. Among rare congenital hemorrhagic diseases, hemophilia represents the condition with the highest consumption and expenditure and the highest annual increase in cost; therefore, many individuals may not have access to clotting factor concentrates (CFCs) due to high costs and limited resources[7]. The high cost of care in hemophilia is due to lifelong treatment, management of complications, ongoing therapeutic advancement[8,9] and is estimated to be accounted for about 90% by the cost of clotting factors[10]. Indeed, it is now well known that a trough plasma level of 1-2 IU/mL is no longer sufficient to provide adequate protection, and intravenous treatment is a barrier to prophylaxis[11,12]. Since 2017, to meet these clinical needs and to increase compliance, treatment options for hemophilia have expanded even more with the advent of extended half-life CFCs (EHL-CFCs), non-replacement therapies administered subcutaneously and gene therapy[13,14]. Thanks to advancements in treatment approaches, bleeding episodes and bleeding rates –previously the most useful clinical outcome indicators (COIs)– are no longer suitable to compare the efficacy of new therapies[15-18]. Therefore, questions about economic sustainability within the national healthcare system are raised, and the best measurable patient-report outcome indicators and assessment tools are searched[19,20]. Assigning economic weight to standard and new outcomes so that regulators can better understand whether increased spending is justified by increased patient well-being remains a challenge. With this in mind, Cortesi *et al.* selected a set of health outcome indicators (three clinical outcome indicators, COIs and five patient-reported outcomes indicators, PROIs) to support a value-based approach to assessing the quality of care in hemophilia[21]. In this context and in line with the concepts expressed in the Regional Diagnostic, Therapeutic, and Care Pathway (PDTA), we conducted a study at the Regional Reference Center for Inherited Bleeding Disorders, University Hospital of Turin, Italy. The study aimed to review clinical outcomes and overall expenditure in 2017 and 2023 in a large cohort of patients, focusing on those who switched medication during the observation period to examine the impact of emerging treatments and new standard of care on well-being and budget.

MATERIALS AND METHODS

The FAR-BENE (pharmacoeconomic and clinical well-being in hemophilia) study was approved by the Ethics Committee of the City of Health and Science of Turin and conducted following good clinical practice and local regulatory requirements. This is a retrospective, no-profit, non-interventional, single-center study conducted at the Adult Regional Reference Center for Congenital Hemorrhagic Disease in Turin. The observation window spans from January 2017 to December 2023. The decision to focus on 2017 and 2023 was made because the vast majority of patients switched drug classes during these years due to progressive availability of new products (*Online Supplementary* **Table SI**).

All therapeutic choices were shared with patients after analysis of new drugs opportunities, wishes and unmet needs; during periodic check-ups after the switch, patient satisfaction was assessed, and adjustments in terms of posology, infusion frequency or type of drug were introduced. Subjects with severe hemophilia (FVIII/FIX <1%) were included. Patients with missing clinical follow-up data, those with an observation period at our Hemophilia Centre of less than 12 months, those who died during the observation period or those lost to follow-up were excluded. For the sub-analysis of patients who switched drug, patients were included if there was at least 12 months follow-up after the switch. Patients with very poor compliance –defined as treatment plan renewal delays of more than 2 months or no contact with the Center for more than 12 months– were excluded from

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the sub-analysis. Expenditure analysis was based on the consumption of CFCs (units or milligram) for each patient during prophylaxis and for bleeding treatment. These counts were done in duplicate and rechecked by the Center's Pharmacists.

The outcomes chosen to define patient's clinical well-being included: number of infusions per year, annualized bleeding rate (ABR), pain assessment via numeric rating scale (NRS), hemophilia joint health score (HJHS), and joint ultrasound score according to the HEAD-US (Hemophilia Early Arthropathy Detection with Ultra Sound) protocol. Additionally, trough plasma levels of factor VIII and factor IX, and therapy-related complication (inhibitor development, infections and thromboembolic events) were recorded. All patients were assigned to treatment regimens based on pharmacokinetics assessment conducted according to expert recommendations[22].

A comprehensive analysis of the whole cohort of patients was performed. Additionally, patients were divided into subgroups for further analysis; patients with HA who switched from plasma-derived concentrates to recombinant concentrate (Group 1) and those with HB who did the same (Group 2); patients with HA who switched from standard half-life CFCs (SHL-CFCs) to EHL-CFCs (Group 3) and those with HB who did the same (Group 4); patients who switched from on-demand treatment to prophylaxis (Group 5); and patients who switched to emicizumab (Group 6). The latter group included 3 patients with inhibitors.

Statistical analysis

Descriptive statistics included absolute frequencies and proportions for categorical variables, second (median), first, and third quartiles for continuous one. The Wilcoxon Sum Rank test examined the statistical significance differences between paired measurements (pre [T0] *vs* post [T1]). All statistical tests were two-sided, with the significance level set at $p<0.05$. Analyses were performed using the R software environment for statistical computing (version 4.2; R Foundation, Wien, Austria).

RESULTS

Eighty patients with severe hemophilia are followed at the hemophilia treatment center in Turin. A total of 70 patients (age >18 years) with severe hemophilia were included in the study, 58 with severe HA and 12 with severe HB. Three patients had inhibitors at the time of switch. The median age at the time of data collection (2023) was 41.5 years and all patients were male. The median weight was 75,0 kg (IQR 65,0-82,0) and remaining unchanged between 2017 and 2023 considering that this is an adult population. Eighteen patients (26%) were unable to perform self-infusion. Six patients had a need for central venous catheter (CVC) for depletion of venous access in 2017, while in 2023, only 3 patients maintained a CVC by necessity. Charlson Comorbidity Index (CCI) changed from 2017 to 2023, but this variation was not statistically significant.

In 2017, the total expenditure was € 12,947,580.44, with a median cost per kilogram per year (€/kg/year) of € 2,458. In 2023, total expenditure increased to € 12,967,576.92, with a median cost of € 2,461 €/kg/year.

During the observation period, 11 patients with HB and 42 patients with HA switched their prophylactic drugs or switched from on-demand treatment to prophylaxis treatment.

Of the 53 patients who made the switch, four were excluded for non-compliance, and four were excluded because the follow-up period after the therapy switch was shorter than 12 months, resulting in a total of 45 patients analyzed (**Figure 1**). Three patients enrolled in interventional clinical trials were included, with their prophylaxis costs fully covered by the sponsor.

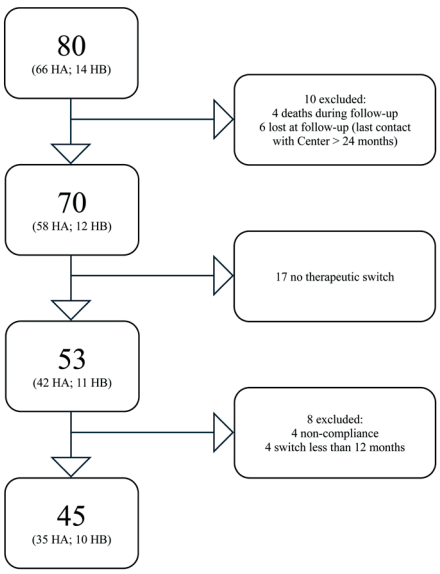


Figure 1 - Study flow-chart

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Concerning the 45 patients analyzed, the center's expenditure in 2017, when no patients had switched medication, was € 9,212,485.81, while in 2023, with patients switching medications, it was € 9,233,977.05. The median annual expenditure per patient increased from € 194,376 in 2017 to € 197,460 in 2023 (p=0.245), with a median cost per kg/year increasing from € 2,456 to € 2,886. The median number of infusions per year significantly decreased from 156 to 91 (p<0.001), ABR from 1 to 0 (p<0.001) and NRS from 3,5 to 0 (p<0.001). As measured by the HJHS and HEAD-US scores, joint health did not show improvement with a slight but not statistically significant increase (HJHS from 10 to 15, p=0.629; HEAD-US from 7 to 8, p=0.774). The median trough level increased from 3 IU/mL to 5 IU/mL (p=0.181), this data does not include patients who switched to emicizumab.

Neither inhibitor appearance nor thromboembolic events were recorded during the observational period. In a subanalysis, patients with HA and HB were analyzed separately (**Table I**). The total expenditure for HA patients was € 10,195,630.17 in 2017 and € 9,073,793.45 in 2023. For HB patients, the expenditure was € 1,307,681.76 in 2017 and € 2,209,577.40 in 2023. Specifically, the median €/kg/y was € 2,990 for HA patients and € 1,601 for HB patients in 2017, while in 2023, it was € 2,840 for HA patients and € 3,204 for HB patients. Clinical outcomes are summarized in **Table I** and in *Online Supplementary* **Table SII**.

Patients were further grouped for analysis based on homogeneous treatment regimens (**Table II**).

Group 1

Four patients were included in group 1, all patients were able to self-infuse, never needed CVC and had no history of inhibitors. The median age in 2023 was 34,5 years and the median weight was 67,5 kg, remaining unchanged between 2017 and 2023.

The total expenditure increased from € 525,560 pre-switch to € 738,734 post-switch (**Figure 2**). In this group, the number of infusions per year significantly decreased, from a median of 182 infusions to 97.5 (p=0.019). Regarding ABR, it increased from 0 to 0.5 (p=0.405); this change was not statistically significant. The NRS decreased from 5 to 1 (p=0.208). Concerning joint health, the HJHS increased from 6 to 20 (p=0.248), while the HEAD-US score increased from 6 to 7.5 (p=0.481), with both changes not reaching statistical significance. Finally, the trough level increased from 2.8 IU/mL to 3.45 IU/mL (p=0.480), showing no significant difference.

Group 2

In Group 2 were included 7 patients with a median age in 2023 of 37,0 years, without history of inhibitors. All patients were able to self-infuse and did not require CVC in their disease history. The median weight of these patients changed from 71,0 kg in 2017 to 70,0 kg in 2023 (p=0.095). The total expenditure significantly increased from € 643,871 pre-switch to € 1,726,516 post-switch (**Figure 2**). In this group, the number of infusions per year decreased significantly, from a median of 104 to 36 (p=0.061). Regarding ABR, it showed significant improvement, decreasing from 4 to 0 (p=0.023). The NRS increased

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Table I - *Sub-analysis of hemophilia A and hemophilia B patients*

	Hemophilia A (No.=35)			Hemophilia B (No.=10)		
	T0	T1	p-value	T0	T1	p-value
No. inf/y	156 [156; 182]	104 [91.0; 120]	<0.001	104 [104; 156]	40.0 [36.0; 52.0]	0.018
€/pts/y	198,432 [105,014; 288,522]	197,460 [133,288; 269,801]	0.769	113,824 [63,180; 172,515]	222,376 [177,309; 263,736]	0.049
€/kg/y	2,990 [1,305; 3,551]	2,840 [2,051; 3,156]	0.805	1,601 [932; 2446]	3,204 [2,572; 3,609]	0.041
Trough	3.00 [1.45; 5.00]	3.95 [1.70; 5.75]	0.609	5.20 [3.45; 9.50]	10.0 [7.00; 13.0]	0.060
ABR	1.00 [0.00; 4.00]	0.00 [0.00; 0.00]	<0.001	5.00 [1.00; 6.00]	0.00 [0.00; 0.75]	0.009
HJHS	10.0 [6.00; 17.2]	16.0 [8.50; 21.5]	0.329	17.0 [6.00; 18.0]	10.5 [4.50; 19.2]	0.461
NRS	4.00 [2.00; 5.50]	0.00 [0.00; 2.50]	<0.001	3.00 [1.00; 6.00]	1.50 [0.00; 3.75]	0.257
HEAD-US	7.00 [4.00; 12.0]	8.00 [5.75; 13.2]	0.787	16.5 [9.50; 22.8]	8.50 [4.25; 16.5]	0.283

N. inf/y: number of infusions per year; € /pts/y: median cost per patient per year; € /kg/y: median cost per kilogram per year; ABR: annualized bleeding rate; HJHS: hemophilia joint health score; NRS: numeric rating scale; HEAD-US: Hemophilia Early Arthropathy Detection with Ultra Sound; T0: pre-switch; T1: post-switch.

Table II - *Sub-analysis by treatment group*

	Group 1 (No.=4)			Group 2 (No=7)			Group 3 (No=16)			Group 4 (No=2)			Group 5 (No=5)			Group 6 (No=11)		
	T0	T1	p	T0	T1	p	T0	T1	p	T0	T1	p	T0	T1	p	T0	T1	p
No. inf/y	182 [176; 228]	97.5 [91.0; 108]	0.019	104 [104; 156]	36.0 [36.0; 52.0]	0.061	169 [156; 182]	112 [91.0; 120]	<0.001	104 [104; 104]	73 [73; 73]	/	52.0 [52.0; 52.0]	73.0 [67.0; 82.0]	0.180	138 [101; 156]	0.00 [0.00; 0.00]	<0.001
€/pts/y	84,000 [72,800; 142,590]	149,485 [133,341; 200,827]	0.149	84,240 [49,140; 118,260]	224,532 [208,120; 263,736]	0.004	233,575 [197,496; 291,681]	187,455 [143,750; 242,569]	0.142	235,795.32 [143,407.68; 328,182.96]	330,690.00 [330,690.00; 330,690.00]	/	62,400 [50,400; 67,600]	50,400 [4,200; 105,300]	0.530	195,000 [152,320; 433,978]	276,322 [238,576; 298,224]	0.221
€/kg/y	1,244 [1,120; 1,784]	2,210 [2,051; 2,612]	0.149	1,053 [797; 1,756]	3,297 [3,033; 3,548]	0.003	3,420 [3,029; 3,691]	2,641 [2,151; 3,144]	0.065	3,618.40 [2,108.94; 5,127.86]	5,167.03 [5,167.03; 5,167.03]	/	824 [813; 843]	813 [51.2; 1284]	0.530	2,434 [1,751; 5,718]	3,106 [2,880; 3,247]	0.279
Trough	2.80 [2.65; 6.40]	3.45 [2.30; 5.00]	0.480	6.50 [3.25; 10.5]	10.0 [7.00; 12.5]	0.174	3.00 [2.40; 4.00]	5.00 [2.00; 6.40]	0.446	5 [4.3; 5.7]	17 [17; 17]	/	0.00 [0.00; 0.00]	0.60 [0.50; 1.80]	0.180	2.25 [0.83; 5.78]	/	/
ABR	0.00 [0.00; 0.25]	0.50 [0.00; 1.50]	0.405	4.00 [1.00; 6.00]	0.00 [0.00; 0.50]	0.023	0.50 [0.00; 1.50]	0.00 [0.00; 0.00]	0.006	3 [1.5; 4.5]	0.5 [0.25; 0.25]	/	15.0 [12.0; 24.0]	0.00 [0.00; 1.00]	0.052	1.00 [0.00; 7.00]	0.00 [0.00; 0.00]	0.013
HJHS	6.00 [4.00; 8.00]	20.0 [13.0; 21.5]	0.248	11.5 [5.50; 17.2]	6.00 [3.00; 15.5]	0.566	9.00 [6.50; 13.5]	10.5 [7.25; 15.8]	0.549	35 [35; 35]	31 [31; 31]	/	23.0 [16.5; 34.0]	28.0 [24.0; 31.0]	0.827	11.0 [6.00; 19.2]	17.0 [10.5; 22.5]	0.619
NRS	5.00 [4.00; 5.50]	1.00 [0.00; 3.00]	0.208	2.50 [1.25; 5.25]	3.00 [0.00; 3.50]	0.512	3.00 [0.00; 5.00]	0.00 [0.00; 3.00]	0.071	5.5 [4.75; 6.25]	2.5 [1.25; 1.25]	/	3.00 [0.00; 7.00]	0.00 [0.00; 2.00]	0.264	4.00 [2.50; 6.50]	0.00 [0.00; 1.50]	0.002
HEAD-US	6.00 [5.50; 6.50]	7.50 [6.25; 11.2]	0.481	11.0 [8.00; 16.5]	5.00 [4.00; 12.0]	0.368	7.00 [4.00; 12.0]	7.00 [6.00; 12.0]	0.904	25 [25; 25]	22 [22; 22]	/	/	12.0 [12.0; 12.0]	/	9.00 [4.50; 24.0]	9.50 [3.50; 19.8]	0.744

N. inf/y: number of infusions per year; €/pts/y: median cost per patient per year; €/kg/y: median cost per kilogram per year; ABR: annualized bleeding rate; HJHS: hemophilia joint health score; NRS: numeric rating scale; HEAD-US: Hemophilia Early Arthropathy Detection with Ultrasound; T0: pre-switch; T1: post-switch. Group 1: Plasma-derived to recombinant (hemophilia A); Group 2: Plasma-derived to recombinant (hemophilia B); Group 3: standard half-life clotting factor concentrates to extended half-life clotting factor concentrates (hemophilia A); Group 4: standard half-life clotting factor concentrates to extended half-life clotting factor concentrates (hemophilia B); Group 5: on demand to prophylaxis; Group 6: switch to emicizumab.

slightly, from 2.5 to 3 (p=0.512), but this change was not statistically significant. The HJHS decreased from 11.5 to 6 (p=0.566), while the HEAD-US score decreased from 11 to 5 (p=0.368). The trough levels increased from 6.5 IU/mL to 10 IU/mL (p=0.174).

Group 3

The Group 3 was the largest group with 16 patients included. All patients were able to self-infuse, never needed CVC and had no history of inhibitors. The median age in 2023 was 35,5 years and median weight increased from 68,5 kg in 2017 to 73,0 kg in 2023 (p=0.042).

In this group expenditure was € 3,702,180 pre-switch and € 3,181,425 post-switch (**Figure 2**). Contextually, the number of infusions per year decreased significantly from 169 to 112 (p<0.001). The ABR decreased from 0.5 to 0 (p=0.006), showing significant improvement. The NRS decreased from 3 to 0 (p=0.071). The HJHS increased from 9 to 10.5 (p=0.549), showing no significant change. The HEAD-US score remained unchanged from 2017 to 2023. Finally, the trough levels increased from 3 IU/mL to 5 IU/mL (p=0.446).

Group 4

In this group only 2 patients were included without history of inhibitor, able to self-infuse without the need for CVC. Age in 2023 was 38,2 years for first patient and 44,8 years for the second. Weight slightly decrease from 67,2 kg in 2017 to 65 kg in 2023 for first patient and from 67,8 kg to 67,0 kg respectively for the second patients.

For the small sample size of Group 4, descriptive statistics are shown in **Table II** and **Figure 2**.

Group 5

In group 5 were included five patients without history of inhibitors. One of them was unable to self-infuse so before the switch he needed a CVC, which was removed after the switch. The median age in 2023 was 65,0 years and median weight decrease from 75,0 kg in 2017 to 74,0 kg in 2023 (p=0.374).

For patients who switched from on-demand treatment to prophylaxis in Group 5, expenditure decreased from € 397,039 to € 273,011 (**Figure 2**). In this group, the number of infusions per year increased from 52 to 73 (p=0.763). The ABR decreased from 15 to 0 (p=0.052). The NRS decreased from 3 to 0 (p=0.264), although this reduction was not statistically significant. The HJHS increased from 23 to

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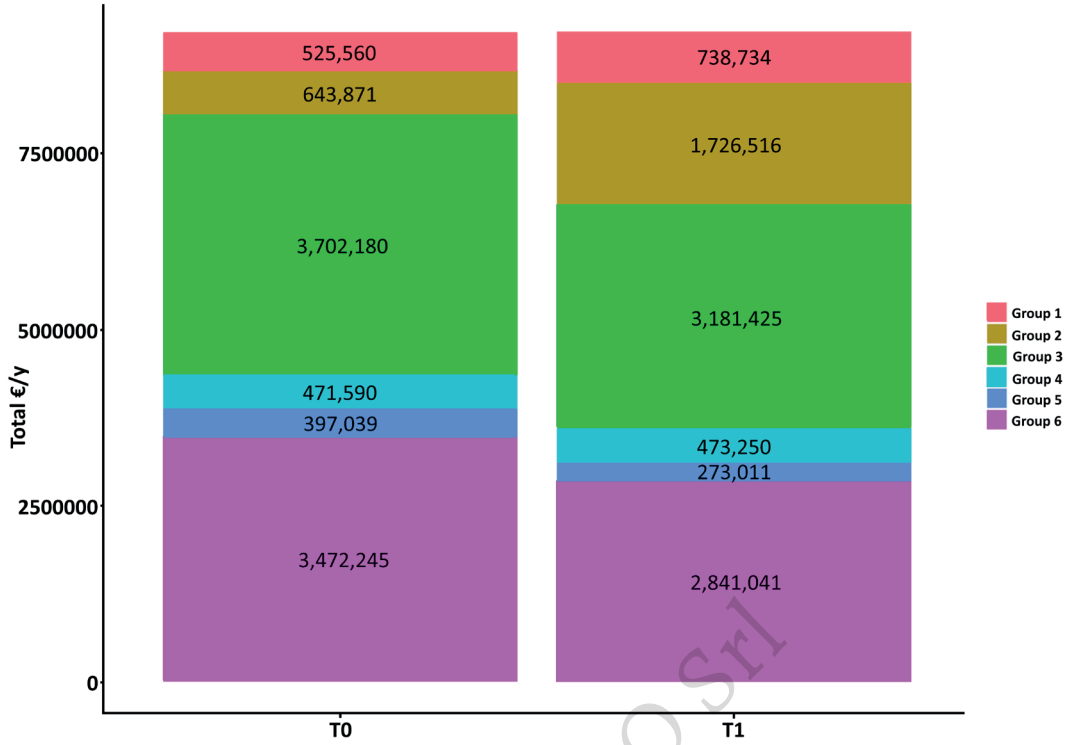


Figure 2 - Total center expenditure
Total €/y: total expenditure per year; T0: pre-switch (2017); T1: post switch (2023); Group 1: plasma-derived to recombinant (hemophilia A); Group 2: plasma-derived to recombinant (hemophilia B); Group 3: standard half-life clotting factor concentrates to extended half-life clotting factor concentrates (hemophilia A); Group 4: standard half-life clotting factor concentrates to extended half-life clotting factor concentrates (hemophilia B); Group 5: on demand to prophylaxis; Group 6: switch to emicizumab.

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28 (p=0.827); this change was not statistically significant. The HEAD-US score could not be compared due to the lack of pre-prophylaxis data.

Group 6

The group 6 consists of 11 patients, 3 with inhibitors at the time of switch and 8 with no history of inhibitor; 54,5% (6/11) of them were unable to self-infuse and 3 patients in 2017 had the need for a CVC. In 2023, only one of them maintained the need for CVC. The median age in 2023 was 57 years and the median weigh was 83 kg, remaining unchanged between 2017 and 2023.

For patients who initiated emicizumab in Group 6, the total expenditure decreased from € 3,472,245 to € 2,841,041 (**Figure 2**). The number of infusions decreased to zero (p<0.001). The ABR decreased from 1 to 0 (p=0.013), indicating significant improvement. The NRS decreased from 4 to 0 (p=0.002), showing statistically significant improvement. The HJHS increased from 11 to 17 (p=0.619). The HEAD-US score increased slightly from 9 to 9.5 (p=0.744). As previously noted, a trough comparison was not conducted for patients in this group.

All data are summarized in **Table II**.

DISCUSSION

Starting from the principle that in the era of individualized and personalized treatment, the relative value of therapies derives from the comparison of outcomes relevant for patients and not only from costs of therapy[21] and based on previous evidence of cost reduction with switches to single EHL product[23,24], our project aims to analyze both clinical outcomes and economic burden in an Italian Reference Centre for Hemophilia.

In this study, we focused on patients with severe hemophilia, as they represent the group with the highest economic impact and the greatest burden in terms of

disease-related complications and comorbidities[10,25]. Even if surgical expenses (especially orthopedic surgeries) and rehabilitation could be encountered in the cost of illness, here we assess the cost of prophylaxis and bleeding treatment concerning patient well-being. Therefore, surgical expenses were excluded from overall calculation.

An overview of all hemophilic population treated at the Center shows a stable cost of therapy, a significant reduction of all three parameters in the area of PROs (ABR, NRS, number of infusion) and non-significant modification of two COIs (HJHS and HEAD US score) and no safety signals were recorded in all patients. In each subgroup, we have recorded an improvement of at least two parameters of the PRO area with a significant reduction of the number of infusions in all groups but group 5, which is consistent with the category of patients who switched from on-demand to prophylaxis therapy.

Notably, NRS decreases in all subgroups but group 2, since pain must be a driver of intervention, particularly in adults in agreement with new indications in monitoring hemophilia[16].

HJHS and HEAD US scores do not show a significant change, notably a slight decrease is recorded only in group 2, where the switch to EHL-CFCs results in median trough level of 10 IU/mL in agreement with a more protective effect on arthropathy[12,26] with higher troughs.

The slight increase of HJHS and HEAD score during our follow up is unfortunately reasonable in light of data published so far: once joint damage has occurred, it will progress over the lifetime even if no bleeds occur in affected joints. Further most of our patients have started tertiary prophylaxis and for these patients the objective of treatment is slowing progression of joint disease, reducing pain and maintaining mobility[27,28]. However few data on evolution of arthropathy are still available from EHL and emicizumab, pivotal trial were not drawn to monitor arthropathy with HJHS and HEAD US; therefore, several years of follow up are needed to assess the real role of new products in the progression of joint damage[29].

In HA groups (1 e 3), trough levels aim to 3-5% as recommended in Kreuth V Initiative[30] and are comparable to previously published switch experiences[31,32] as expression of the best performances of present FVIII EHL-CFCs. Overall, in accordance with the same recommendations mentioned above[30], 65% and 50% of patients who switched to a EHL-CFCs (HA and HB) achieved a trough greater than or equal to 3% and 5%, respectively.

Concerning the HEAD-US score, the observation period following the therapeutic switch varied within our patient groups. Determining the optimal timing for follow-up ultrasound assessments to detect significant changes remains an ongoing area of research, and the time period in our study could be unsuitable for detecting changes.

Furthermore, in Group 3 (patients with HA who changed treatment from SHL-CFCs to EHL-CFCs) even if trough levels did not increase significantly, the reduction in the number of infusions was associated with an improvement in NRS and ABR. This could indirectly suggest an improvement in therapeutic adherence[33].

In group 5, the cost reduction, is caused by the reduction in ABR and consequently in the total number of units administered. Indeed, the prophylactic regimen leads to an increase in the number of infusions with fewer units per infusion because the infusions are not necessary to treat an ongoing bleeding. Primary and secondary prophylaxis were also found to be cost-effective compared with ondemand therapy in models in the literature[34].

Finally, for Group 6 (patients who switched to emicizumab prophylaxis), a slight, non-significant worsening of joint status was observed. Still, we must underline that switch was necessary for all patients because of venous access problems. Without an alternative therapeutic strategy, compliance would have been compromised with a feasible worsening of all parameters and patient well-being.

The just published report of the Medicines Utilization Monitoring Centre (*Osservatorio Nazionale sull'Impiego dei Medicinali* [OsMed])[35] on use of drugs in Italy shows that coagulation products still represent 2,1% of overall public expenditure and a further per capita increase of 1,7% has been recorded in 2023 compared to 2022. Here we report an unvaried cost in our population. However, the OsMed report is a comprehensive evaluation. Our analysis that focuses on cost of prophylaxis and bleedings in a single center highlights stable expenditure: these results are due to a different approach (cost/patient instead of cost/inhabitant; cost of treatment instead of global cost) and to an analytical examination of single patient trend, that reflects daily interest and commitment in the best treatment of our patients along with a better

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use of economic public resources, that is the final aim of hemophilia centers.

Previous studies considered the impact of treatment choice on the hemophilia center's budget and the patient's clinical well-being; however, in some cases these are cost estimation models and not real costs[24,36,37], others compared a single product or a class of products with the previous therapeutic regimen[38-40], and still others not consider clinical outcomes such as joint status and pain[41,42]. Our study for the first time globally considers the management of a hemophilia center in Italy, taking into account both real expenditures and the clinical outcomes that are most important in defining the well-being status of the hemophilia patient.

However this study has limitations, including its retrospective nature, the absence of assessment of quality of life (QoL), a single-Center design of the trial, the lack of assessment at the same timepoint for each patient after the switch due to the pandemic and the failure to quantify of hemophilia-related costs (e.g., hospitalization costs for bleeding episodes and/or complications, surgical and rehabilitation expenses, CVC-related costs, and so on) as well as indirect costs expressed in terms of school/ work days lost.

CONCLUSIONS

Our study is the first attempt at a comprehensive analysis of the impact of therapeutic choice on well-being and economic burden of care in a Hemophilia Center using implemented set of outcome indicators. However, our data suggest that it will be increasingly important to balance the economic benefits with the well-being of patients. A simple mathematical calculation of costs fails to value the improvement in outcomes produced by therapeutic innovation. Further evaluating the cost for an individual patient without considering the Center's global context could be misleading. Therefore, it is necessary to validate and give economic weight to the best tools of patient welfare than can be included in the economic calculation for better quantification of expenditure. Previously, the literature focused on clinical aspects or pharmaco-economics; here, for the first time, both have been considered in real-world clinical practice to assess the disease's economic impact. Data from other settings (e.g., other centers or other countries) would be useful.

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AUTHORSHIP CONTRIBUTION

Conceptualization: CS and AB. Methodology: AB. Data curation: RP, AP, MS and DC. Validation: CD, FV and AB. Investigation: FV, CD, RP, AV, GM, and SB. Writing-original draft preparation: CS. Writing-review and editing: CS, AB, and AP. Visualization: GS and RA. Supervision: BB and AB. All Authors have read and agreed to the published version of the manuscript.

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REFERENCES

1. Mannucci PM, Tuddenham EGD. The hemophilias - From royal genes to gene therapy. N Engl J Med. 2001; 344(23): 1773-1779. doi: 10.1056/NEJM200106073442307.
2. Giampaolo A, Abbonizio F, Arcieri R, Hassan HJ. Italian Registry of Congenital Bleeding Disorders. J Clin Med. 2017; 6(3): 34. doi: 10.3390/jcm6030034.
3. Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, et al. Guidelines for the management of hemophilia. Haemophilia. 2013; 19(1): e1-e47. doi: 10.1111/j.1365-2516.2012.02909.x.
4. Mancuso ME, Mahlangu JN, Pipe SW. The changing treatment landscape in haemophilia: from standard half-life clotting factor concentrates to gene editing. Lancet. 2021; 397(10274): 630-640. doi: 10.1016/S0140-6736(20)32722-7.
5. Manco-Johnson MJ, Abshire TC, Shapiro AD, Riske B, Hacker MR, Kilcoyne R, et al. Prophylaxis versus Episodic Treatment to Prevent Joint Disease in Boys with Severe Hemophilia. N Engl J Med. 2007; 357(6): 535-544. doi: 10.1056/NEJMoa067659.
6. Hermans C, Noone D, Benson G, Dolan G, Eichler H, Jiménez-Yuste V, et al. Hemophilia treatment in 2021: Choosing the"optimal" treatment using an integrative, patient-oriented approach to shared decision-making between patients and clinicians. Blood Rev. 2022; 52: 100890. doi: 10.1016/j.blre.2021.100890.
7. Verma SP, Dutta TK, Mahadevan S, Nalini P, Basu D, Biswal N, et al. A randomized study of very low-dose factor VIII prophylaxis in severe haemophilia – A success story from a resource limited country. Haemophilia. 2016; 22(3): 342-348. doi: 10.1111/hae.12838.
8. Di Minno MN, Di Minno G, Capua MD, Cerbone AM, Coppola A. Cost of care of haemophilia with inhibitors. Haemophilia. 2010; 16(1): e190-e201. doi: 10.1111/j.1365-2516.2009.02100.x.
9. Marano G, Da Cas R, Zito S, Ippoliti I, Fortinguerra F, Pierantozzi A, et al. [Hemophilia A Therapy: expenditure and consumption for the year 2022 and future spending scenarios]. Available at: https://europepmc.org/article/med/37114608. Accessed on: 05/05/2023. [in Italian].
10. Thorat T, Neumann PJ, Chambers JD. Hemophilia burden of disease: a systematic review of the cost-utility literature for hemophilia. J Manag Care Spec Pharm. 2018; 24(7): 632-642. doi: 10.18553/jmcp.2018.24.7.632.

11. Collins PW, Blanchette VS, Fischer K, Björkman S, Oh M, Fritsch S, et al. Break-through bleeding in relation to predicted factor VIII levels in patients receiving prophylactic treatment for severe hemophilia A. J Thromb Haemost. 2009; 7(3): 413-420. doi: 10.1111/j.1538-7836.2008.03270.x.
12. Den Uijl IEM, Fischer K, Van Der Bom JG, Grobbee DE, Rosendaal FR, Plug I. Analysis of low frequency bleeding data: the association of joint bleeds according to baseline FVIII activity levels. Haemophilia. 2011; 17(1): 41-44. doi: 10.1111/j.1365-2516.2010.02383.x.
13. Mancuso ME, Croteau SE, Klamroth R. Benefits and risks of non-factor therapies: Redefining haemophilia treatment goals in the era of new technologies. Haemophilia. 2024; 30(S3): 39-44. doi: 10.1111/hae.14976.
14. Manco-Johnson MJ, Warren BB. Long-term prophylaxis: what are our options and how to define success? Hematology Am Soc Hematol Educ Program. 2022; 2022(1): 579-585. doi: 10.1182/hematology.2022000397.
15. Konkle BA, Skinner M, Iorio A. Hemophilia trials in the twenty-first century: Defining patient important outcomes. Res Pract Thromb Haemost. 2019; 3(2): 184-192. doi: 10.1002/rth2.12195
16. Manco-Johnson MJ, Warren BB, Buckner TW, Funk SM, Wang M. Outcome measures in Haemophilia: Beyond ABR (Annualized Bleeding Rate). Haemophilia. 2021; 27(S3): 87-95. doi: 10.1111/hae.14099.
17. van Balen EC, O'Mahony B, Cnossen MH, Dolan G, Blanchette VS, Fischer K, et al. Patient-relevant health outcomes for hemophilia care: Development of an international standard outcomes set. Res Pract Thromb Haemost. 2021; 5(4): e12488. doi: 10.1002/rth2.12488.
18. Dover S, Blanchette VS, Srivastava A, Fischer K, Abad A, Feldman BM. Clinical outcomes in hemophilia: towards development of a core set of standardized outcome measures for research. Res Pract Thromb Haemost. 2020; 4(4): 652-658. doi: 10.1002/rth2.12331.
19. Castaman G, Jimenez-Yuste V, Gouw S, D'Oiron R. Outcomes and outcome measures. Haemophilia. 2024; 30 (S3): 112-119. doi: 10.1111/hae.14990.
20. Minno MNDD, Martinoli C, Pasta G, la Corte-Rodriguez H, Samy I, Stephensen D, et al. How to assess, detect, and manage joint involvement in the era of transformational therapies: role of point-of-care ultrasound. Haemophilia. 2023; 29(1): 1-10. doi: 10.1111/hae.14657.
21. Cortesi PA, Fornari C, Conti S, Pollio B, Boccalandro E, Buzzi A, et al. The value-based healthcare approach to haemophilia: Development of outcome measures for the evaluation of care of people with haemophilia. Haemophilia. 2024; 30(2): 437-448. doi: 10.1111/hae.14943.
22. Associazione Italiana dei Centri Emofilia. [Principles of treatment and updated recommendations for hemophilia A and B replacement therapy]. Available at: https: //aiceonline.org/wp-content/uploads/2019/02/Raccomandazioni-per-la-Terapia-Sostitutiva-dellemofilia-A-e-B-AICE-2017_approvato.pdf. [in Italian]. Accessed on 17/05/2018.
23. Bidlingmaier C, Heller C, Langer F, Miesbach W, Scholz U, Oldenburg J, et al. Real-world usage and effectiveness of recombinant factor VIII/factor IX Fc in hemophilia A/B: final data from the 24-month, prospective, noninterventional PREVENT study in Germany. Res Pract Thromb Haemost. 2024; 8(5): 102482. doi: 10.1016/j.rpth.2024.102482.
24. Iorio A, MacDonald V, Caillaud A, Luckevich MD, Christoffersen P, Matino D, et al. Treatment switch to nonacog beta pegol factor IX in hemophilia B: A Canadian cost-consequence analysis based on real-world factor IX consumption and clinical outcomes. Res Pract Thromb Haemost. 2023; 7(3): 100106. doi: 10.1016/j.rpth.2023.100106.
25. Zhou ZY, Koerper MA, Johnson KA, Riske B, Baker JR, Ullman M, et al. Burden of illness: direct and indirect costs among persons with hemophilia A in the United States. J Med Econ. 2015; 18(6): 457-465. doi: 10.3111/13696998.2015.1016228.
26. Gualtierotti R, Solimeno LP, Peyvandi F. Hemophilic arthropathy: current knowledge and future perspectives. J Thromb Haemost. 2021; 19(9): 2112-2121. doi: 10.1111/jth.15444.
27. Kuijlaars I a. R, Timmer MA, de Kleijn P, Pisters MF, Fischer K. Monitoring joint health in haemophilia: Factors associated with deterioration. Haemophilia. 2017; 23(6): 934-940. doi: 10.1111/hae.13327.
28. Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. Blood. 2015; 125(13): 2038-2044. doi: 10.1182/blood-2015-01-528414.
29. Rodriguez-Merchan EC. Synovitis in hemophilia: preventing, detecting, and treating joint bleeds. Expert Rev Hematol. 2023; 16(7): 525-534. doi: 10.1080/17474086.2023.2209717.
30. Peyvandi F, Berger K, Seitz R, Hilger A, Hecquet ML, Wierer M, et al. Kreuth V initiative: European consensus proposals for treatment of hemophilia using standard products, extended half-life coagulation factor concentrates and non-replacement therapies. Haematologica. 2020; 105(8): 2038-2043. doi: 10.3324/haematol.2019.242735.
31. Peyvandi F, Garagiola I, Boscarino M, Ryan A, Hermans C, Makris M. Real-life experience in switching to new extended half-life products at European haemophilia centres. Haemophilia. 2019; 25(6): 946-952. doi: 10.1111/hae.13834.
32. Tagliaferri A, Matichecchia A, Rivolta GF, Riccardi F, Quintavalle G, Benegiamo A, et al. Optimising prophylaxis outcomes and costs in haemophilia patients switching to recombinant FVIII-Fc: a single-centre real-world experience. Blood Transfus. 2020: 374-385. doi: 10.2450/2019.0220-19.
33. Pedra G, Christoffersen P, Khair K, Lee XY, O'Hara S, O'Hara J, et al. The impact of factor infusion frequency on health-related quality of life in people with haemophilia. J Haem Pract. 2020; 7(1): 102-109. doi: 10.17225/jhp00158.
34. Unim B, Veneziano MA, Boccia A, Ricciardi W, La Torre G. Haemophilia A: pharmacoeconomic review of prophylaxis treatment versus on-demand. ScientificWorldJournal. 2015; 2015: 596164. doi: 10.1155/2015/596164.
35. AIFA. [The Medicines Utilization Monitoring Centre - *Osservatorio Nazionale sull'Impiego dei Medicinali* (OsMed) - 2023 Report]. Available at: https: //www.aifa.gov.it/documents/20142/2594020/AIFA_Rapporto%20OsMed_2023.pdf. Accessed on 11/06/2025. [in Italian].
36. Sun SX, Wu Y, McDermott M, van Keep M. Cost-effectiveness model of recombinant FVIII versus emicizumab treatment of patients with severe hemophilia A without inhibitors. Blood. 2019; 134 (Suppl_1): 2102. doi: 10.1182/blood-2019-124421.
37. Kragh N, Tytula A, Pochopien M, Aballéa S, Toumi M, Hakimi Z, et al. Cost-effectiveness of recombinant factor VIII Fc versus emicizumab for prophylaxis in adults and adolescents with haemophilia A without inhibitors in the UK. Eur J Haematol. 2023; 110(3): 262-270. doi: 10.1111/ejh.13901.
38. Rodríguez López M, Megías Vericat JE, Albo López C, Bonanad S. Clinical, pharmacokinetic and economic analysis of the first switch to an extended half-life factor IX (albutrepenonacog alfa, rFIX-FP) in Spain. BMJ Case Rep. 2020; 13(10): e234142. doi: 10.1136/bcr-2019-234142.
39. Yu JK, Wong WWL, Keepanasseril A, Iorio A, Edginton AN. Cost-utility analysis of emicizumab for the treatment of severe hemophilia A patients in Canada. Haemophilia. 2023; 29(2): 488-497. doi: 10.1111/hae.14723
40. Aiello A, Mancuso ME, Leone S, Rossi L, Cioni L, Teruzzi C. Cost analysis of extended half-life recombinant factor IX products in the treatment of haemophilia B in Italy: an update. Glob Reg Health Technol Assess. 2022; 9: 9-13. doi: 10.33393/grhta.2022.2331.
41. Samelson-Jones BJ, Guelcher C, Kuhn J, Butler R, Massey G, Guerrera MF, et al. Real-world cost estimates of initiating emicizumab in US patients with haemophilia A. Haemophilia. 2021; 27(4): 591-598. doi: 10.1111/hae.14347.
42. Escobar M, Agrawal N, Chatterjee S, Bhattacharya S, Caicedo J, Bullano M, et al. Impact of switching prophylaxis treatment from factor VIII to emicizumab in hemophilia A patients without inhibitors. J Med Econ. 2023; 26(1): 574-580. doi: 10.1080/13696998.2023.2196922.

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