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REAL-WORLD ANNUAL BLEEDING RATE IN PEOPLE WITH SEVERE HEMOPHILIA A WITHOUT INHIBITOR ON PROPHYLAXIS, COMPARING SWITCHED TO rFVIII-Fc VERSUS NON-SWITCHED PATIENTS: A MULTICENTER, RETROSPECTIVE, NON INTERVENTIONAL, BEFORE-AFTER STUDY WITH THE FRENCH BERHLINGO DATABASE (MOTHIF-II)

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Declaration Of Interest:

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PURPOSE / OBJECTIVES

According to the pivotal studies, factor VIII (FVIII) with extended half-life (EHL) efmoroctocog alfa (rFVIII-Fc) could influence the management of prophylaxis, while maintaining good clinical efficacy on the occurrence of bleeding events (BE). What about in reality? The MOTHIF-II study explored **FVIII prophylaxis and the impact on the annual bleeding rate (ABR) in patients with Severe Hemophilia A without current inhibitor** (pwSHA) in Western France, further to the availibility of the rFVIII-Fc.

MATERIALS & METHODS

We investigated pwSHA followed in **7 Hemophilia Treatment centers (HTC) of the BERHLINGO Group** (Angers, Brest, Caen, Le Mans, Nantes, Rennes and Tours), **before and after the rFVIII-Fc supply** (2x12 months: T1 = 07-2015/06-2016 versus (vs) T2 = 06-2017/07-2018). Self-treated BE (pains included) were collected from the patients' traceability logbooks; only complete records on T1 & T2 were eligible. We compared the **ABR and the amounts of FVIII needed to treat BE for matched patients on prophylaxis** (same patients ⇔ before/after).

RESULTS

A total of **88 pwSHA** had a complete traceability logbook for both study periods and **697 self-treated BE** were recorded. No significant difference was globally observed in the ABR between T1 & T2 on the whole cohort. Nevertheless, **for switched patients (rFVIII-Fc only during T2), a significant decrease of the ABR and of the amount of FVIII injected to treat BE** was noted: ABR from 6.6 to 4.0 & 40% drop in FVIII required (See Table 1 - Wilcoxon signed-rank test, α=5%, p=0.003 for ABR, p=0.028 for FVIII). The **ABR of switched patients became comparable to that of patients on standard half-life FVIII (SHL FVIII):** 4.0 vs 3.3. Seventeen patients had an ABR = 0 during T1 & T2 (whom 71% were on SHL FVIII on both periods). Eight patients became ABR negative during T2; 63% of them had switched to rFVIII-Fc.

Self-treated bleeding events were dominated by three major categories: **hemarthrosis, hematomas and pain** (See Figure 1). The hemorrhagic profile remained identical for each of the 3 subgroups of patients studied, between T1 and T2. The **ankles** emerged as the main joints at risk for both hemarthrosis and pain.

For switched patients, the hemorrhagic profile was also different comparatively to patients on SHL FVIII, with **a higher ABR at baseline** and a **significantly bigger proportion of hemarthroses** (48% of total treated events vs 29% for non-switched people – See Table 2). Their **AJBR** was also three times higher at the outset, **with the switch to rFVIII-Fc leading to its significant decrease from 3.2 to 1.9** (See Table 2 – Wilcoxon signed-rank test, α=5%, p=0.033 for AJBRs).

MOTHIF II study (ABR): key points

Does rFVIII-Fc have an impact on the ABR and the amount of FVIII required to treat bleeding events in real-life, for pwSHA without inhibitor, on prophylaxis, in comparison with SHL FVIII?

Non-interventional, retrospective, before/after, uncontrolled, open label study

T1: SHL FVIII for all → rFVIII-Fc available → T2: switched & non-switched pwSHA

88 pwSHA whom*:

BERHLINGO centers (France)
On prophylaxis
With complete
Traceability logbooks
on T1/T2

	Treatment unchanged: SHL FVIII (N = 49 patients)		Switch to rFVIII-Fc only (N = 25 patients)
ABR (T1 vs T2)	3.2 vs 3.3		**6.6 vs 4.0**
AJBR (T1 vs T2)	0.9 vs 0.9	SIMILAR	SIGNIFICANT → **3.2 vs 1.9**
FVIII for bleeding events (T1 vs T2) [IU/year/patient]	⇗ 10% 9,201 vs 10,092 IU		⇘ **40%** **22,818 vs 12,957 IU**

**Results of 14 patients who switched during T2 not presented here*

The pwSHA on prophylaxis switched to rFVIII-Fc were the ones who initially bled the most and had the highest proportion of hemarthrosis!

↳ Switching to rFVIII-Fc significantly reduced their ABR/AJBR, and consequently, the amount of FVIII required to treat these BE!

This study is part of the French network of University Hospitals HUGO ("Hôpitaux Universitaires du Grand Ouest"). It was funded by the Sobi pharmaceutical laboratories as an Investigator Sponsor Study (ISS).

RESULTS

Table 1: description of ABR and FVIII administered for bleeding events in matched patients, before and after switch to rFVIII-Fc (according to the type of FVIII prescribed over T2)

Matched patients on prophylaxis, complete traceability logbook (n = 88)		SHL FVIII only during T1 & T2 (N = 49 patients)	SHL FVIII during T1 and rFVIII-Fc only during T2 (N = 25 patients)	SHL FVIII during T1 and switch from SHL FVIII to rFVIII-Fc during T2 (N = 14 patients)
T1	Weight in kg (mean +/- sd)	52.7 +/- 24.4	48.8 +/- 21.5	49.0 +/- 34.0
	Treated events (n)	157	165	62
	ABR / patient / year (mean +/- sd)	3.2 +/- 4,4[a]	**6.6 +/- 6,9[b]**	4.4 +/- 5.0
	FVIII for ABR (IU/patient/year) (mean +/- sd)	9,201 +/- 14,057[a]	**22,818 +/- 26,119[b]**	10,346 +/- 19,448
T2	Weight in kg (mean +/- sd)	56.2 +/- 21.5	53.3 +/- 19.7	51.9 +/- 32.4
	Treated events (n)	164	100	49
	ABR / patient / year (mean +/- sd)	3.3 +/- 4.5[a]	**4.0 +/- 5.5[b]**	3.5 +/- 3.4
	FVIII for ABR (IU/patient/year) (mean +/- sd)	10,092 +/- 13,436[a]	**12,957 +/- 16,552[b]**	*9,308 +/- 12,816*

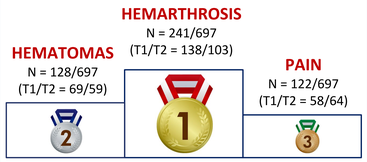
[a] Wilcoxon signed-rank test, non significant α = 5%; [b] Wilcoxon signed-rank test, significant α = 5% (p = 0.003 for ABR & p = 0.028 for administered FVIII)

Table 2: ABR and AJBR in matched patients on prophylaxis (switched to rFVIII-Fc vs non-switched, with complete traceability logbooks)

Matched patients on prophylaxis, complete traceability logbook	SHL FVIII only over T2 (N = 49)		rFVIII-Fc only over T2 (N= 25)	
	T1	T2	T1	T2
Patients with ABR = 0 (n)	14	15	3	7
Patients with ABR ≠0 *(n)* / Total of treated bleeding events (n)	35 / 157	34 / 164	22 / 165	18 / 100
→ ABR	→ 3.2[a]	→ 3.3[a]	→ **6.6[b]**	→ **4.0[b]**
> BE = hemarthrosis: patients (n) / treated hemarthrosis (n, % of total BE))	17 / 46 (29%)	19 / 45 (27%)	12 / 79 (48%)	10 / 47 (47%)
→ AJBR	→ 0.9[a]	→ 0.9[a]	→ **3.2[b]**	→ **1.9[b]**

[a] Wilcoxon signed-rank test, non significant α = 5% (ABR vs ABR & AJBR vs AJBR);
[b] Wilcoxon signed-rank test, significant α = 5% (p =0.003 for ABRs and p = 0.033 for AJBRs)

Figure 1: self-treated bleeding events
(n = 88 patients / 697 events)



- *Hemarthrosis: ankles (37%), elbows (24%), knees (17%), hips (2%)…*
- *Hematomas: biceps (13%), forearms (8%), quadriceps (7%) , knees (6%)…*
- *Pain: ankles (19%), knees (17%), elbows (11%), wrists (6%)…*

CONCLUSION

Our study showed a significant improvement in the hemorrhagic phenotype in patients treated with rFVIII-Fc. Patients with high baseline ABR and mainly self-treated for hemarthrosis seem to have been the priority targets for switching to rFVIII-Fc. Only real-life studies are likely to show such results.

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