What we learn from data of a prospective post-authorization safety surveillance study in 384 hemophilia A patients with antihemophilic factor (recombinant) plasma / albumin free method demonstrates safety and efficacy in Japan

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Introduction

Post-Authorization Safety Surveillance Study (PASS) is essential for the evaluation of safety in the real life clinical practice settings. Data of Japanese PASS of ADVATE [Antihemophilic Factor (Recombinant) Plasma/Albumin Free Method: rAHF-PFM] collected under Japanese ordinance Good Post-Marketing Study Practice (GPSP) may reflect the current treatment situation of a person with hemophilia A.

Currently, target trough level is one of the discussion points when we consider personalized prophylaxis treatment. Actual experience data is valuable for the consideration and for future comparison with newly developed products.

Objective

To review data for both product safety, i.e. inhibitor development in hemophilia A patients treated with rAHF-PFM, and influence factors on quality of the patients' life including on-demand and prophylaxis treatments.

Methods

This prospective, multicenter, observational surveillance study was conducted at 101 sites from February 2007 to June 2012 to investigate hemophilia A of any age and disease severity, with ≥4 exposure days (EDs) at study entry, who were prescribed rAHF-PFM, reviewed as of March 2014.

- Treatment was based on investigator's prescription
- Prophylaxis definition was more than 1 infusion per week and over 4 weeks in analysis .

Results

Subjects Characteristics (Table 1)

- Of 384 subjects receiving the rAHF-PFM more than once, 341 (89%) completed two years of observation and 43 subjects were withdrawn before two years.
- Age of first rAHF-PFM infusion was 25.3±17.5 years (mean ±SD) and 24.0 years (median, range 0-81).
- 55.5% had experience of prophylaxis treatment before entry, 62.5% in severe, and 37.0% in moderate.
- 58.1% [(50+173)/384] as total had joint dysfunction (JD) (1 joint: 13.0%, ≥ 2 joints: 45.1%). It was similar in severe (1 joint: 13.2%, ≥ 2 joints: 46.2%), and moderate (1 joint: 15.1%, ≥ 2 joints: 47.9%).

Table 1: Subject Characteristics at entry

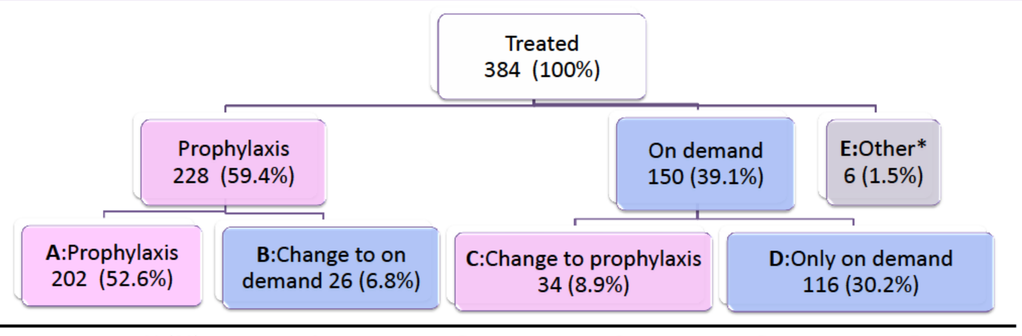
	all	severe	moderate	mild	unknown
N (%)		< 1 %	1 - 5 %	5 % <	
# of subjects	384 (100.0)	288 (75.0)	73 (19.0)	21 (5.5)	2 (0.5)
EDs at entry					
4 - 50	42 (10.9)	17 (5.9)	10 (13.7)	15 (71.4)	0 (0.0)
≥ 51	342 (89.1)	271 (94.1)	63 (86.3)	6 (28.6)	2 (100.0)
Median age of first rAHF-PFM use	24.0	21.0	27.0	37.0	48.5
Inhibitor History	36* (9.4)	33* (11.5)	3 (4.1)	0 (0.0)	0 (0.0)
Experience of prophylaxis before entry	213 (55.5)	180 (62.5)	27 (37.0)	4 (19.0)	2 (100.0)
joint dysfunction					
1 joint	50 (13.0)	38 (13.2)	11 (15.1)	1 (4.8)	0 (0.0)
≥ 2 joints	173 (45.1)	133 (46.2)	35 (47.9)	4 (19.0)	1 (50.0)
Hepatic Disease	158 (41.1)	118 (41.0)	28 (38.4)	10 (47.6)	2 (100.0)

*Of those, 6 subjects had inhibitor at entry.

Treatment

- Of 228 subjects started on prophylaxis at entry, 202 subjects continued prophylaxis. Fifteen of 26 subjects who changed from prophylaxis to on demand re-started prophylaxis during this study period.
- Of 150 subjects who started on-demand therapy at entry, 34 subjects switched to prophylaxis.
- Median total infusion and total usage per subject were 222 infusions and180, 250IU on prophylaxis and 44 infusions and 50,500 IU on demand.

Figure 1: Disposition of subjects by treatment during study and ABR



	N (%)	A	B	C	D	E
severe	288 (100.0)	169 (58.7)	21 (7.3)	23 (8.0)	72 (25.0)	3 (1.0)
moderate	73 (100.0)	28 (38.4)	3 (4.1)	9 (12.3)	32 (43.8)	1 (1.4)
mild	21 (100.0)	3 (14.3)	2 (9.5)	2 (9.5)	12 (57.1)	2 (9.5)
median age	(y)	14.5	33.5	22.0	34.0	30.0
joint dysfunction : ≥1		99 (49.0)	16 (61.5)	22 (64.7)	82 (70.7)	4 (66.7)
ABR in all (median)	prophylaxis	4.0	6.3	3.0	-	1.4
	on demand	-	24.0	19.8	24.8	-

*Other includes subjects with only operation and prophylaxis with <1 per week.

Annualized Bleeding Rate (ABR) by regimen and FVIII severity

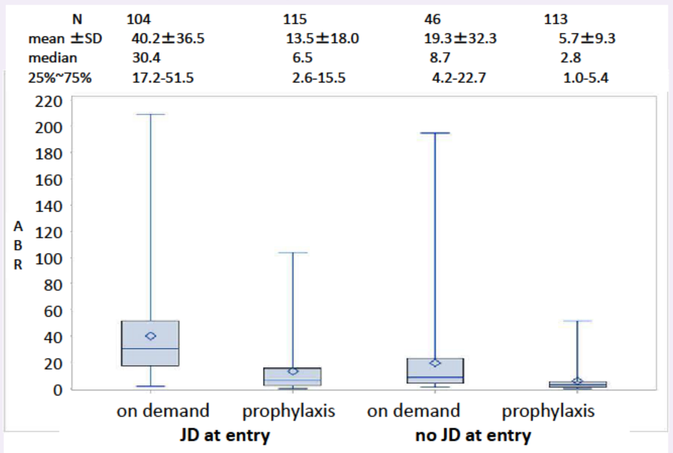
- Median ABR was lower in prophylaxis treatment in both with JD (6.5) and without JD (2.8) at entry. Some subjects with JD and on demand treatment reported high ABR. (Figure 2a)
- Of 202 prophylaxis continued subjects, 58 (28.7%) had less than 2 bleeding episodes and 19 (9.4%) had 0 bleeding.
- Subjects treated with prophylaxis 3 times per week tend to have a lower median ABR. (Table 2)
- Median ABR in moderate subjects with on demand was as much as in severe subjects. (Figure 2b)
- Prophylaxis improved over 50% reduction of ABR in 70% (24/34) but didn't improve in 15% (5/34). (Figure 3)

Table 2: Dose/kg/infusion and ABR in subjects with prophylaxis

Regimen	N	dose/kg per infusion median	dose/kg per infusion IQR	ABR median	ABR IQR
all	228	20.0*	(16.7-26.3)	4.05	(1.50-10.72)
1/week	35	18.0	(15.2-21.9)	5.41	(3.00-17.94)
2/week	78	20.0	(16.7-25.4)	4.72	(1.64-10.98)
≥3/week	115	21.3*	(16.7-27.0)	3.25	(1.00-8.98)

*Body weight data were missing in 2 subjects.

Figure 2a: ABR in prophylaxis and on demand treatment (JD/no JD)



Median ABR are indicated with horizontal bars. The vertical bars indicate the range of max-min and horizontal boundaries of boxes represent the first and third quartiles. Mean are indicated with rhombus . JD: Joint dysfunction

Figure 3: ABR in changed group

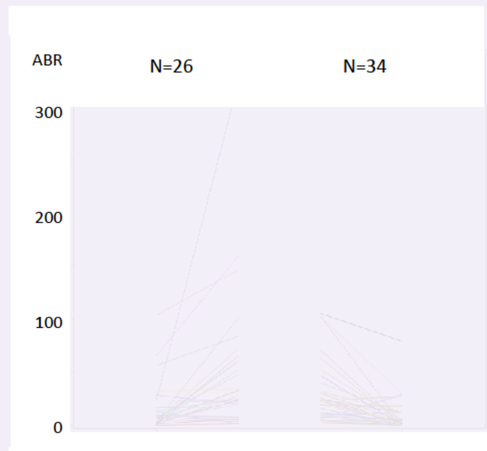
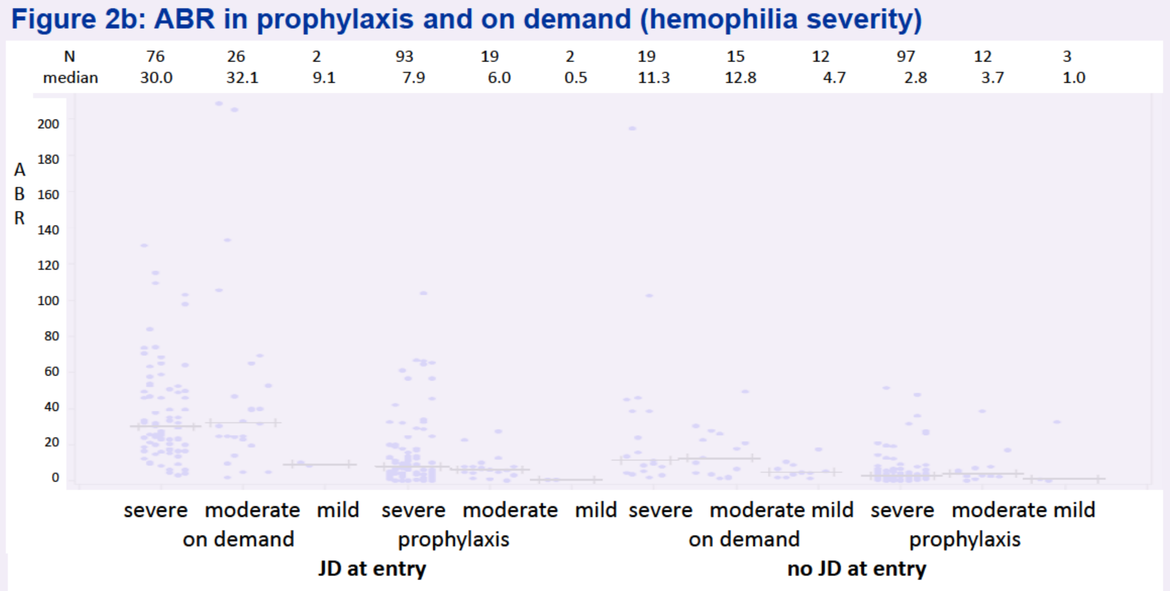


Figure 2b: ABR in prophylaxis and on demand (hemophilia severity)



Safety

- Of 36 subjects with an inhibitor history, 30 subjects (negative status at entry) did not develop recurrent inhibitors and 1 of 6 with inhibitors at entry had an increase in titer from 5 BU/mL to 33 BU/mL after ITI.
- Three of 39 subjects with ≤ 50 EDs and no inhibitor history at entry developed low-titer inhibitor (7.69%). No *de novo* inhibitor developed in 309 subjects with ≥ 51ED (0%) (Table 3).
- No inhibitor was detected in subjects who switched from pd-VIII or 2nd generation rFVIII to rAHF-PFM.

Table 3: Inhibitor development in subjects without inhibitor history

EDs at entry	4 ～50 EDs N=39				51 ～ EDs N=309			
Inhibitor at diagnosis	No of subject inhibitor developed	%	95% CI		No of subject inhibitor developed	%	95% CI	
High titer (＞5BU)	0	0.00	(0.00	7.39)	0	0.00	(0.00	0.96)
Low titer (1≦≦5BU)	2	5.13	(0.63	17.32)	0	0.00	(0.00	0.96)
Other (＜1BU)	1	2.56	(0.06	13.48)	0	0.00	(0.00	0.96)
Total	3	7.69	(1.62	20.87)	0	0.00	(0.00	0.96)

Conclusions

- Joint dysfunction at entry in moderate subjects was similar to in severe subjects.
- Median ABR in prophylaxis treatment was lower than on demand treatment in both the JD and no JD groups.
- Median ABR in moderate subjects was similar to median ABR in severe in on demand group with or without JD at entry.
- Prophylaxis improved over 50% reduction of ABR in 67% (23/34) but didn't improve in 14% (5/34).
- 3 of 39 (7.7%) minimally treated (4-50 EDs at entry) subjects without inhibitor history developed low-titer inhibitor.
- No *de novo* inhibitor were reported in subjects with ≥ 51EDs at entry who switched to rAHF-PFM.
- This result further supports the safety profile of rAHF-PFM in a large Japanese hemophilia A population.
- An individualized approach for treatment including prophylaxis for both severe and moderate subjects should be considered.

References

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If you have any additional questions, please feel free to contact Baxter Bioscience Medical Information at medinfo@baxter.com.

Conflicts of interest:

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