Comparability of bleeding outcomes by prophylactic FVIII replacement intensity: A post hoc analysis of a noninterventional study of men with severe hemophilia A

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Introduction

- The prospective, noninterventional study 270-902 collected real-world data on outcomes of a global cohort of people with severe hemophilia A receiving regular exogenous factor VIII (FVIII) prophylaxis[1]
- For participants in the study, the intensity of prophylactic treatment varied widely and may have impacted the results[1]
- The aim of this post hoc analysis was to describe bleeding outcomes for those receiving high- and low-intensity prophylactic FVIII replacement in study 270-902

Methods

- 270-902 was a multicenter, multinational, longitudinal noninterventional study that served as the lead-in for a Phase 3 trial of valoctocogene roxaparvovec gene therapy
  - Participants provided 6 months of retrospective data at baseline. During the study, up to 12 months of prospective data on rates of bleeding and FVIII use were collected by participant self-report
- Participants were adult men (≥18 years) with severe hemophilia A (FVIII ≤1 IU/dL) and no history of inhibitors who were receiving prophylactic FVIII replacement for ≥6 months prior to study entry
- For this post hoc analysis, adeno-associated virus serotype 5 total antibody-negative participants with ≥6 months follow-up were stratified by annualized FVIII utilization for prophylaxis per the third edition of the World Federation Hemophilia treatment guidelines at baseline[2]
  - Low-dose prophylaxis was defined as <4000 IU/kg/year
  - High-dose prophylaxis was ≥4000 IU/kg/year
- Mean annualized bleeding rate (ABR) and proportion of participants with zero bleeds were compared when considering both all bleeds and bleeds that were followed by FVIII treatment
- Significance was assessed with a 2-sample t-test for continuous variables and a chi-square test for categorical variables. Missing data were not imputed

Results

- Among 194 participants, mean (SD) baseline annualized FVIII utilization was 5499.6 (1751.4) and 2838.0 (705.7) IU/kg/year and mean annualized FVIII infusion rate was 145.7 (42.0) and 120.2 (46.0) infusions per year for high-dose and low-dose intensity cohorts, respectively
  - Geographic region, extended half-life (EHL) and standard half-life (SHL) product use, and history of HIV infection differed significantly between cohorts; baseline characteristics were otherwise similar (**Table 1**)

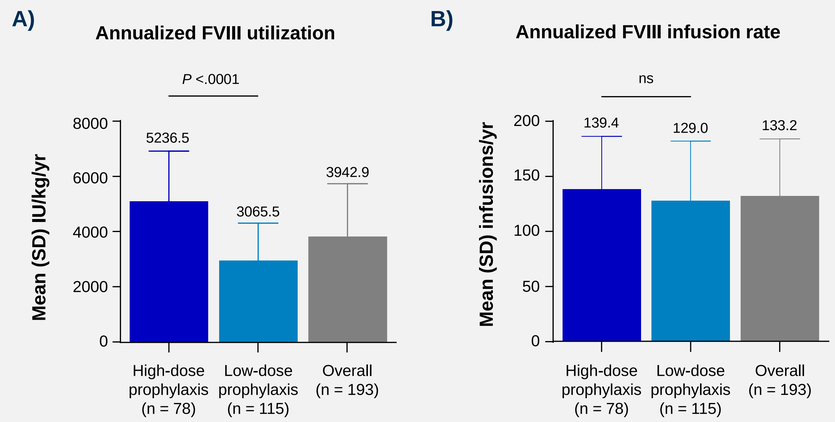
Table 1. Patient demographics and baseline characteristics by intensity of prophylaxis

Parameter	High-dose prophylaxis[a] ≥4000 IU/kg/yr (n = 78)	Low-dose prophylaxis[a] <4000 IU/kg/yr (n = 116)	Overall (n = 194)	*P*-value
Age at enrollment, median (min, max) yrs	32 (18, 70)	30 (18, 71)	31 (18, 71)	.6697
Region				
Australia	10 (12.8)	13 (11.2)	23 (11.9)	
Europe/Middle East[b]	29 (37.2)	37 (31.9)	66 (34.0)	
South America[c]	5 (6.4)	26 (22.4)	31 (16.0)	<.0001
East Asia[d]	7 (9.0)	11 (9.5)	18 (9.3)	
North America[e]	22 (28.2)	7 (6.0)	29 (14.9)	
Africa[f]	5 (6.4)	22 (19.0)	27 (13.9)	
Weight, mean (SD), kg	78.7 (18.1)	79.7 (17.4)	79.3 (17.7)	.7538
History of hepatitis B[g], n (%)	14 (17.9)	15 (12.9)	29 (14.9)	.3365
History of hepatitis C[g], n (%)	33 (42.3)	43 (37.1)	76 (39.2)	.4636
History of HIV, n (%)	6 (7.7)	2 (1.7)	8 (4.1)	.0404
Participants with problem joints[h], n (%)	28 (35.9)	31 (26.7)	59 (30.4)	.1733
Annualized FVIII usage, mean (SD) IU/kg/yr[i]	5499.6 (1751.4)	2838.0 (705.7)	3908.1 (1797.9)	<.0001
AFR, mean (SD) infusions/yr	145.7 (42.0)	120.2 (46.0)	130.5 (46.0)	.0001
Prior blood coagulation factor use, n (%)[j]	78 (100.0)	116 (100.0)	194 (100.0)	
SHL products only	36 (46.2)	66 (56.9)	102 (52.6)	<.0001
EHL products only	24 (30.8)	15 (12.9)	39 (20.1)	
ABR – all bleeds, mean (SD) bleeds/yr	5.2 (9.6)	6.0 (11.2)	5.7 (10.6)	.5977
ABR – treated bleeds, mean (SD) bleeds/yr[i]	4.9 (9.0)	5.6 (10.4)	5.3 (9.8)	.5947
Participants with zero bleeds – all bleeds, n (%)	30 (38.5)	47 (40.5)	77 (39.7)	.7742
Participants with zero bleeds – treated bleeds, n (%)	32 (41.0)	49 (42.2)	81 (41.8)	.8663

[a]During the baseline period. [b]Belgium, Germany, Spain, France, UK, Israel, and Italy. [c]Brazil. [d]Korea and Taiwan. [e]USA. [f]South Africa. [g]Includes cleared or cured infections. [h]Problem joints were identified by investigators at baseline and were defined as joints with any of the following symptoms: chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding. [i]6-month period before Day 1 visit. [j]Medications taken within 30 days prior to Day 1 visit were included. Continuous variables are evaluated with a 2-sample t-test, and categorical variables are evaluated with a chi-square test. ABR, annualized bleeding rate; AFR, annualized infusion rate; EHL, extended half-life; FVIII, factor VIII; HIV, human immunodeficiency virus; SD, standard deviation; SHL, standard half-life; yr, year.

- Overall, median (range) follow-up time for bleeding outcomes was 223 (171–469) days
- Throughout follow-up, mean annualized FVIII utilization was 5236.5 (1665.9) and 3065.5 (1188.4) IU/kg/year in the high- and low-dose cohorts (**Figure 1A**)
  - Despite a significant difference in annualized FVIII infusion rate between the two cohorts at baseline, there was no difference on-study (**Figure 1B**)

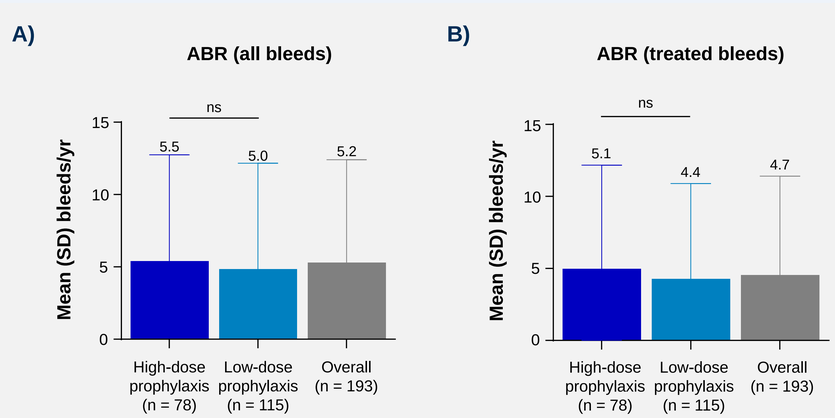
Figure 1. FVIII use during the on-study period. A) Annualized FVIII usage. B) Annualized FVIII infusion rate



Significance was assessed with a two-sample t-test. High-dose prophylaxis was defined as ≥4000 IU/kg/yr; low-dose prophylaxis was defined as <4000 IU/kg/yr. FVIII, factor VIII; ns, not significant; SD, standard deviation; yr, year.

- Mean calculated ABR for all bleeds was 5.52 (7.22) and 4.96 (7.19) in the high- and low-dose cohorts, respectively; absolute difference in mean ABR for all bleeds was 0.56 (*P* = .6001) (**Figure 2A**)
- Mean calculated ABR for treated bleeds was 5.09 (7.08) and 4.38 (6.52) in the high- and low-dose cohorts, respectively; absolute difference in mean ABR for treated bleeds was 0.71 (*P* = .4761) (**Figure 2B**)

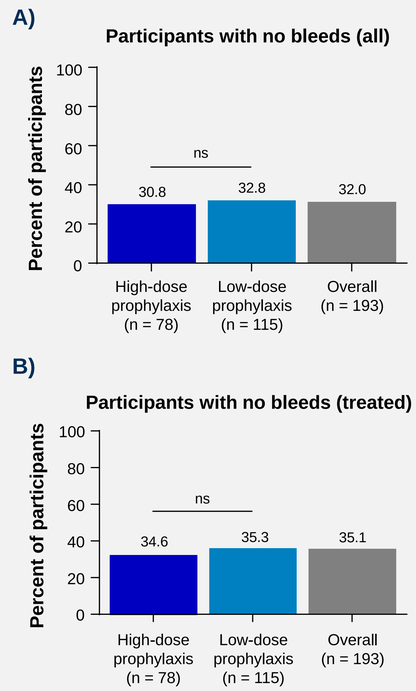
Figure 2. ABR during the on-study period for A) all bleeds and B) only treated bleeds



Significance was assessed with a two-sample t-test. High-dose prophylaxis was defined as ≥4000 IU/kg/yr; low-dose prophylaxis was defined as <4000 IU/kg/yr. ABR, annualized bleeding rate; ns, not significant; SD, standard deviation; yr, year.

- In the high- and low-dose cohorts, 30.8% and 32.8% of participants, respectively, had no bleeds regardless of whether treatment was administered. The absolute difference between cohorts was not significant (**Figure 3A**)
- Absolute difference in proportion of participants with zero treated bleeds was 0.7% (high-dose, 34.6% vs low-dose, 35.3%; *P* = .9168) (**Figure 3B**)

Figure 3. Proportion of participants with zero bleeds when considering A) all bleeds and B) only treated bleeds



Significance was assessed with a chi-square test. High-dose prophylaxis was defined as ≥4000 IU/kg/yr; low-dose prophylaxis was defined as <4000 IU/kg/yr. ns, not significant; yr, year.

Conclusions

- Irrespective of FVIII consumption, bleeding risks remain and were found similar across the cohorts
- Cohorts stratified by prophylaxis intensity differed by geographic region, use of EHL or SHL product, and history of HIV; relative levels of activity/risk are unknown

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References

1. Kenet, G, et al. *J Clin Med.* 2021 Dec 18;10(24):5959; 2. Srivastava, A, et al. *Haemophilia.* 2020 Aug;26 Suppl 6:1-158.

Disclosures

All authors are employees and stockholders of BioMarin Pharmaceutical Inc.

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