A review of recommended factor doses administered, and annual bleed rate relative to adherence level in a population with hemophilia A and B

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Introduction and Objectives:

- While prophylactic treatment of hemophilia has been definitively linked with improved joint health outcomes [1], few studies exist to support the hypothesis that non-adherence to prophylaxis leads to increased joint bleeding
- The Validated HEmophilia RegImen Treatment Adherence Scale – PROphylaxis (VERITAS-Pro) is a reliable, validated measure of adherence to prophylaxis[2]
- The VERITAS-PRO is a 24-item scale, consisting six 4-item subscales: Time, Dose, Plan, Remember, Skip, and Communicate and results in a total and subscale scores, with higher scores indicating poorer adherence
- The study aimed to test the correlation between VERITAS-Pro scores with: (1) the proportion of recommended doses administered and; (2) annual bleed rate (ABR)

Methods:

Data:

- Study sample was comprised of patients participating in in the VERITAS-Pro validation study (n=66); one patient from the VERITAS-Pro sample was excluded due to lack of infusion log data and chart data other than pharmacy dispensations [2]
- Doses administered were ascertained by infusion logs (n=25)
- Bleeding episodes were extracted from electronic medical records (EMR) maintained by the Indiana Hemophilia and Thrombosis Center (IHTC) (n=66)

Statistical Analysis:

- "Recommended dose" was calculated as: total number of expected prophylaxis doses per week multiplied by study duration (4.3 weeks per month x 3 months)
- Weeks with bleeding episodes were excluded from the "Recommended dose" calculation
- "Off schedule" prophylaxis infusions, such as those prior to physical activities or medical procedures were excluded
- ABR was calculated as the total number of bleeding episodes reported by the patient or documented in the EMR; if both were present, the EMR documentation was used as the primary source of information
  - Patients were categorized as having no bleeding (ABR=0) or having at least one bleed (ABR>0)
- The 70th percentile of the VERITAS-Pro total score was chosen as a clinically useful cutoff score;
  - VERITAS-Pro scores<70th percentile were coded as 0 (good adherence)
  - VERITAS-Pro scores≥70th percentile were coded as 1 (poorer adherence)
- Pearson correlation coefficients were calculated to determine correlation between dose consumption and ABR, and VERITAS-Pro score
- Fisher's exact test (one sided) was used to assess statistical significance in the 70th percentile evaluation and two-sided test was used to assess significance level of recommended dose administered and ABR

Results:

Correlation with recommended dose consumption:

- Twenty five patients were included in the analysis of recommended dose [mean age=16.2 (SD 16.9); 80% severe FVIII deficiency; 4% moderate FVIII deficiency; 16% severe FIX deficiency]
- VERITAS-Pro total score was significantly correlated (r= -0.79, p<0.001) with the proportion of recommended doses administered (Table 1)
- All subscales except Dose were also highly correlated with this measure (r=-0.53 to -0.76)

Correlation with ABR:

- Sixty six patients were included in the analysis of ABR [mean age=15.0 (SD 12.8); 78.8% severe FVIII deficiency; 4.5% moderate FVIII deficiency; 16.7% severe FIX deficiency]
- ABR ranged from 0 to 54 with the median = 1. No significant correlations were observed between the VERITAS-Pro score and ABR (Table 1)
- Analysis of total VERITAS-Pro scores indicated that more patients in the poor adherence group had ABR>0 compared with those in the good adherence group (86% vs. 62% respectively, p=0.046; Table 2)
- Similar results were observed in the Skip subscale, with 88% of patients in the poor adherence group having ABR>0, compared to only 60% of patients with good adherence rate (p=0.015)

Table 1. Pearson Correlations

		Proportion of recommended doses administered (n=25)	ABR per electronic medical record (n=66)
Time	Correlation	-0.678**	-0.030
	Sig. (2-tailed)	<0.001	0.809
Dose	Correlation	-0.281	-0.027
	Sig. (2-tailed)	0.174	0.829
Plan	Correlation	-0.607**	-.090
	Sig. (2-tailed)	0.001	0.472
Remember	Correlation	-0.526*	0.075
	Sig. (2-tailed)	0.007	0.552
Skip	Correlation	-0.690**	0.023
	Sig. (2-tailed)	<0.001	0.853
Communicate	Correlation	-0.758**	-0.017
	Sig. (2-tailed)	<0.001	0.892
Total	Correlation	-0.790**	-0.008
	Sig. (2-tailed)	<0.001	0.947

** *p*<0.001

Table 2. Sample Proportion with >0 Bleeds by 70th Percentile of VERITAS-Pro Score

Subscale	70th Percentile VERITAS-Pro Cutoff Score (>)	Number (%) of Subjects With >0 Bleeds: Score ≤ Cutoff (Good Adherence)	Number (%) of Subjects With >0 Bleeds: Score > Cutoff (Poor Adherence)	Fisher's Exact p (1-tailed)
Time	8	27/43 (63)	19/23 (83)	0.080
Dose	5	29/44 (66)	17/22 (77)	0.257
Plan	7	33/44 (75)	13/22 (59)	0.149
Remember	8	30/46 (65)	16/20 (80)	0.183
Skip	7	25/42 (60)	21/24 (88)	0.015
Communicate	6	28/41 (68)	18/25 (72)	0.487
Total	44	28/45 (62)	18/21 (86)	0.046

Conclusions:

- **This study confirms the relationship between the VERITAS-PRO self reports of adherence and the actual adherence in day-to-day life, demonstrating that each scale area is important in capturing the behaviors associated with adherence.**
- **The fact that there is no clear consistency in the correlation between total or subscale score and ABR is likely associated with the complex interaction among multiple influences (e.g. phenotype) causing or affecting bleeding. The lack of a relationship may also be due to small sample size.**
- **However, the fact that there were significantly more patients with ABR>0 among poor adherence group as compared with good adherence group suggests that it would be premature to rule out any correlation between adherence and ABR.**
- **Further research to quantify the relationship between non-adherence and bleed frequency is needed.**

References:

1. Manco-Johnson, MJ et al. *Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia.* The New England Journal of Medicine, 2007. **357**(6): p. 535-544.
2. Duncan NA et al. *VERITAS-Pro: a new measure of adherence to prophylactic regimens in haemophilia.* Haemophilia, 2010. **16**(2): p. 247-55.

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Disclosure:

Sangeeta Krishnan is an employee and shareholder of Biogen Idec.

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