Joint range of motion findings among female patients with hemophilia A from the ATHNdataset

Martin Chandler,[1] Lena Charafi,[2] Thomas Moulton,[2] Michael Recht[1,3]
[1]American Thrombosis & Hemostasis Network, Rochester, NY, USA; [2]Bayer, Whippany, NJ, USA; [3]Yale University School of Medicine, New Haven, CT, USA

CONCLUSIONS

- **Females are likely underdiagnosed with hemophilia, as evidenced by literature searches and the limited data for this population from the ATHNdataset**
- **These data show that females with hemophilia A have reduced range of motion (ROM) similar to males, despite having near normal Factor VIII levels and mild disease. Joint ROM limitations likely begin prior to adolescence and may reflect the lack of treatment due to underdiagnosis**
  - **With the limited data available, it is suggested that female patients with hemophilia A may have less joint damage in the upper extremities compared with the lower extremities**
- **Females with one abnormal Factor VIII gene should be closely monitored for life at hemophilia treatment centers, and should be classified as having hemophilia if complications arise**
  - **Females should not be diagnosed based on criteria for males, but by phenotype**
- **Additional research, including systematic data on the evolution of joint ROM in females with hemophilia A, is needed**

OBJECTIVES

- **To explore the ROM in females with hemophilia A treated with either BAY 94-9027 (damoctocog alfa pegol, Jivi®, Bayer) or BAY 81-8973 (octocog alfa, Kovaltry®, Bayer) using data from the ATHNdataset**

INTRODUCTION

- Joint bleeding is a major clinical manifestation of hemophilia A[1]
- Repeat bleeding into the joint eventually leads to limited joint mobility, reduced ROM, and arthropathy[2,3]
  - There is also evidence that joint damage can result from even a single joint bleed[3–5]
- Although it is known that joint bleeding is common in males with hemophilia,[2] less is known about the prevalence of joint bleeding and the subsequent morbidity in females with hemophilia A
- A previous study demonstrated that females with Factor VIII deficiency had reduced ROM compared with controls, and that subclinical joint bleeding may be occurring before adolescence[2]
- There is currently a lack of randomized clinical trials in females with hemophilia; thus, real-world databases are important to provide data
- The ATHNdataset is a Health Insurance Portability and Accountability Act-compliant, de-identified database sponsored by the American Thrombosis and Hemostasis Network, including 17,109 patients with hemophilia A

METHODS

- The ATHNdataset was used to identify female patients who received BAY 94-9027 or BAY 81-8973 between January 1, 2010 and April 30, 2022
- Baseline demographics, medical history, and ROM were extracted for female patients with ROM assessment included in their medical record
- ROM data were compared with normative Centers for Disease Control and Prevention (CDC) values for age-matched females[6]
- Results are presented descriptively throughout

RESULTS

- Data for 354 patients receiving BAY 81-8973 were available for this analysis; no data were available for patients receiving BAY 94-9027
- ROM data were available for five of the 13 female patients enrolled in the database who were receiving BAY 81-8973 at the time of analysis (**Table 1**)
  - Baseline Factor VIII levels ranged from 21% to 41%, and all patients had mild disease
- All five female patients had decreased ROM values over multiple joints when compared with normative CDC values (**Table 1**)
- The reduction in joint ROM was more pronounced in the lower-extremity joints compared with the upper-extremity joints, particularly at the ankles, hips, and knees
  - Index joints (ankles, knees, and elbows) are also the most frequently affected joints in males[1]

Table 1: CHARACTERISTICS, MEDICAL HISTORY, AND ROM DATA AVAILABLE IN FEMALES WITH HEMOPHILIA

	43-year-old[a] African American	13-year-old[a] Caucasian	27-year-old[a] Caucasian	25-year-old[a] Hispanic/ Latina	23-year-old[a] African American
	FVIII[b]: 38%	FVIII[b]: 41%	FVIII[b]: 39%	FVIII[b]: 21%	FVIII[b]: 35%
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
	Current treatment: BAY 81-8973 intermittent prophylaxis[c] for 0.38 years **Bleeds on current treatment:** 0 **Previous treatment:** SHL recombinant FVIII concentrate on demand for 14.65 years **Bleeds on previous treatment:** 2 trauma and 3 joint	**Current treatment:** BAY 81-8973 on demand for 2.55 years **Bleeds on current treatment:** 0 **Previous treatment:** Aminocaproic acid on demand for 0.01 years **Bleeds on previous treatment:** 0	**Current treatment:** BAY 81-8973 continuous prophylaxis for 5.04 years **Bleeds on current treatment:** 0 **Previous treatment:** No data **Bleeds on previous treatment:** No data	**Current treatment:** BAY 81-8973 intermittent prophylaxis[c] for 5.02 years **Bleeds on current treatment:** 0 **Previous treatment:** SHL recombinant FVIII concentrate on demand for 9.11 years **Bleeds on previous treatment:** 0	**Current treatment:** BAY 81-8973 on demand for 5.08 years **Bleeds on current treatment:** 0 **Previous treatment:** Recombinant FVIII concentrate intermittent prophylaxis[c] for 1.09 years **Bleeds on previous treatment:** 0

Location	Motion	Normative range (age 20–44/age 9–19)	(2008; 44 years)[d] (left/right ROM)	(2010; 16 years)[d] (left/right ROM)	(2010; 28 years)[d] (left/right ROM)	(2017; 27 years)[d] (left/right ROM)	(2020; 27 years)[d] (left/right ROM)
Shoulder	Flexion	180.0/169.8–173.8	180/180	180/180	180/180	170/166	156/165
Elbow	Flexion	149.1–150.9/ 148.5–150.9	103/145	140/145	130/120	152/152	155/156
Elbow	Supination	80.0–104.0/ 88.0–92.0	80/80	88/90	80/80	75/70	80/80
Elbow	Pronation	81.0–83.0/79.6–82.8	80/80	72/70	80/80	75/75	80/80
Knee	Flexion	140.9–142.9/140.8–143.8	135/135	145/147	124/135	112/118	124/124
Hip	Extension	17.0–19.2/18.6–22.4	27/24	27/28	N/A	10/15	16/21
Hip	Flexion	132.5–135.1/133.0–136.8	120/120	124/123	120/120	122/NA	142/140
Ankle	Dorsiflexion	12.9–14.7/15.6–19.0	20/18	10/10	N/A	8/10	5/10
Ankle	Plantarflexion	60.6–63.6/54.8–59.8	50/50	75/74	35/40	46/50	49/50

[a]Age at first ROM evaluation; [b]Lowest ever FVIII level; [c]Defined as event-based, short-term, or intermittent prophylaxis; [d]Year of and age at most recent ROM evaluation.
Orange boxes indicate abnormal ROM values. FVIII, Factor VIII; NA, not available; ROM, range of motion; SHL, standard half-life

Limitations

- The real-world data in the ATHNdataset were captured during ATHN-affiliated hemophilia treatment center reviews and patients sharing bleeding events at those reviews
- Due to the potentially incomplete nature of such datasets, results from real-world studies could be subject to recall bias
- These limitations should be taken into consideration while interpreting the data presented here

Acknowledgments
The study was sponsored by Bayer US, NJ, USA. Medical writing services were provided by Kennedy Shaw, MSc, of Adelphi Communications Ltd (Bollington, UK), funded by Bayer US in accordance with Good Publications Practice 2022 guidelines.

References
1. Knobe K and Berntorp E. *J Comorb*. 2011;1:51–59. **2.** Sidonio RF *et al*. *Am J Hematol*. 2014;89(8):831– 836. **3.** Gooding R *et al*. *J Blood Med*. 2021;12:209–220 **4.** van Vulpen LF *et al*. *Osteoarthritis Cartilage*. 2015;23(1):63–69. **5.** Vels KK *et al*. BMC *Musculoskelet Disord*. 2020;21(1):241. **6.** Centers for Disease Control and Prevention. Normal Joint Range of Motion Study. Available from: https://www.cdc.gov/ncbddd/jointrom/index.html. Accessed May 10, 2023.

Disclosures
MC, none to declare. LC, Bayer employee. TM, Bayer employee. MR, research funding support to employer from Bayer, BioMarin, CSL Behring, Genentech, Grifols, HEMA Biologics, LFB, Novo Nordisk, Octapharma, Pfizer, Sanofi, Spark, Takeda, uniQure; consultation/advisory board fee from Catalyst Biosciences, CSL Behring, Genentech, HEMA Biologics, Kedrion, Novo Nordisk, Pfizer, Sanofi, Takeda, uniQure; member of the Board of Directors of Foundation for Women and Girls with Blood Disorders, Partners in Bleeding Disorders and employee of ATHN, Oregon Health and Science University.

Poster presented at the ISTH 2023 congress, Montreal, Canada, June 24–28, 2023.