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Surgeries and procedures in people with haemophilia A on emicizumab prophylaxis: analysis from the ATHN 7 haemophilia natural history study

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Summary

ATHN 7 (NCT03619863) is a natural history prospective cohort study of the safety and effectiveness of treatments, including emicizumab, for people with haemophilia A (PwHA) or B in the US

68 participants receiving emicizumab in the ATHN 7 study reported 94 surgeries included in the analysis

Data from this analysis may inform the development of guidelines for the surgical management of PwHA in the future

The majority of major and minor surgeries and procedures were not associated with treated bleeds, consistent with surgeries data from the HAVEN 1–4 trials[1]

Background

- The safety and efficacy of emicizumab prophylaxis has been demonstrated in both clinical and real-world studies. However, additional real-world data from large populations of people with haemophilia A (PwHA) are needed.
- ATHN 7 (NCT03619863) is a natural history prospective cohort study of the safety and effectiveness of treatments, including emicizumab, for PwHA or people with haemophilia B in the US.[2]
- Emicizumab is a bispecific monoclonal antibody that bridges activated FIX and FX to substitute for the function of absent or deficient activated factor (F)VIII in PwHA.[3]
- This analysis characterizes the real-world surgical management and outcomes in ATHN 7 participants receiving emicizumab.

Methods

- ATHN 7 is conducted at 26 American Thrombosis and Hemostasis Network (ATHN)-affiliated sites; eligible participants had a diagnosis of congenital haemophilia A or B and received care at participating sites; no restrictions were placed on haemophilia severity or sex of the participants.
- This analysis was performed solely on PwHA treated with emicizumab prophylaxis.
- Demographic and clinical information was collected at baseline and at least quarterly through participant interview and medical record review.
- Descriptive statistics of medical history and demographic data, as well as longitudinal data, are used to characterize the study population; adverse events were also documented.
- Surgical procedures were classified as major or minor as per Santagostino *et al*.[4]

Participant demographics

- As of 31 August 2022, 78 participants of the ATHN 7 study receiving emicizumab had ≥1 surgery or procedure
  - Of these, 7 surgeries were performed prior to first dose of emicizumab and 6 surgeries were classified as non-invasive; hence, both categories were excluded from this analysis
  - The inhibitor status of two participants is unknown, therefore their data were excluded from this analysis.
- In total, 68 participants who underwent a total of 94 surgeries were included in this analysis (**Table 1**).

Table 1. Baseline demographics and disease history

	Inhibitor (n=18)	Non-inhibitor (n=50)	Overall (N=68)
Age at first surgery, years			
Mean (SD)	16.8 (17.7)	22.5 (18.9)	21.0 (18.7)
Median (Min, Max)	8.0 (2.0, 61.0)	16.0 (0, 71.0)	15.5 (0, 71.0)
Primary diagnosis HA severity, n (%)			
Mild	0 (0)	1 (2.0)	1 (1.5)
Moderate	1 (5.6)	7 (14.0)	8 (11.8)
Severe	17 (94.4)	42 (84.0)	59 (86.8)
Male sex assigned at birth, n (%)	18 (100)	50 (100)	68 (100)
Race, n (%)			
American Indian or Alaska Native	0 (0)	1 (2.0)	1 (1.5)
Asian	0 (0)	2 (4.0)	2 (2.9)
Black or African American	3 (16.7)	1 (2.0)	4 (5.9)
White	13 (72.2)	44 (88.0)	57 (83.8)
Mixed Race*	0 (0)	1 (2.0)	1 (1.5)
Unknown	2 (11.1)	1 (2.0)	3 (4.4)
Ethnicity, n (%)			
Hispanic, Latino/a, or Spanish origin	4 (22.2)	6 (12.0)	10 (14.7)
Not Hispanic, Latino/a, or Spanish origin	13 (72.2)	44 (88.0)	57 (83.8)
Unknown	1 (5.6)	0 (0)	1 (1.5)
Family history of haemophilia, n (%)			
Yes	11 (61.1)	32 (64.0)	43 (63.2)
No	4 (22.2)	14 (28.0)	18 (26.5)
Unknown	3 (16.7)	4 (8.0)	7 (10.3)
Participants undergoing surgery, n (%)			
1 procedure	13 (72.2)	38 (76.0)	51 (75.0)
2 procedures	3 (16.7)	8 (16.0)	11 (16.2)
>2 procedures	2 (11.1)	4 (8.0)	6 (8.8)
Emicizumab exposure prior to first surgery, weeks			
Mean (SD)	55.1 (48.6)	46.9 (32.4)	49.0 (37.2)
Median (Min, Max)	40.9 (0.14, 149)	41.9 (3.29, 114)	41.9 (0.14, 149)
Q1, Q3	12.4, 96.3	15.4, 69.9	14.3, 77.6

*Reported multiple race categories. HA, haemophilia A; Q, quartile; SD, standard deviation.

Surgeries and procedures

- Overall, 11 major surgeries were reported by participants:
  - These were one each of cardiac catheterization, hernia repair, operation on bone of skull, CT angiography of lower limb artery, haemorrhoidectomy, laminectomy, open reduction of closed clavicular fracture, procedure on head, reconstruction of anterior cruciate ligament of knee, replacement of total knee joint, and revision of total knee arthroplasty (all components).
- A total of 24 and 59 minor surgeries were reported in the inhibitor (n=16) and non-inhibitor (n=45) populations, respectively.

Outcomes of major and minor surgeries

- Participants reported a total of 11 major surgeries
  - In PwHA with inhibitors, 0/3 major surgeries were associated with additional factor concentrate or a treated bleed
  - In PwHA without inhibitors, 2/8 (25.0%) major surgeries (total knee joint replacement; reconstruction of anterior cruciate ligament of the knee) were managed with additional factor concentrate and associated with a treated bleed; each participant received standard half-life (SHL) recombinant FVIII concentrate.
- Outcomes for the 83 minor surgeries are shown in **Table 2** and **Table 3**.

Table 2. Outcomes of minor surgeries in participants with FVIII inhibitors

	Inhibitor (n=16)			
	rFVIIa	pdFVIII	SHL FVIII	Other haemostatic agent*
CVAD – 11 procedures				
Number of procedures managed with additional prophylactic factor concentrate (%)	2 (18.2)	2 (18.2)	4 (36.4)	0
Median prophylactic cumulative dose/surgery (Q1, Q3)	†	57.1 IU/kg (51.5, 62.7)	48.4 IU/kg (44.1, 52.6)	N/A
Number of procedures associated with treatment for postoperative bleeds (%)	1 (9.1)	1 (9.1)	1 (9.1)	0
Median cumulative postoperative dose/surgery (Q1, Q3)	†	62.7 IU/kg (62.7, 62.7)	†	N/A
Dental – 7 procedures				
Number of procedures managed with additional prophylactic factor concentrate (%)	4 (57.1)	0	2 (28.6)	2 (28.6)
Median prophylactic cumulative dose/surgery (Q1, Q3)	86.1 µg/kg (81.0, 87.4)	N/A	48.8 IU/kg (44.1, 53.5)	N/A
Number of procedures associated with treatment for postoperative bleeds (%)	2 (28.6)	0	0	2 (28.6)
Median cumulative postoperative dose/surgery (Q1, Q3)	81.0 µg/kg (81.0, 81.0)	N/A	N/A	N/A
ENT – 4 procedures				
Number of procedures managed with additional prophylactic factor concentrate (%)	0	0	3 (75.0)	0
Median prophylactic cumulative dose/surgery (Q1, Q3)	N/A	N/A	51.4 IU/kg (51.4, 76.4)	N/A
Number of procedures associated with treatment for postoperative bleeds (%)	0	0	1 (25.0)	0
Median cumulative postoperative dose/surgery (Q1, Q3)	N/A	N/A	57.3 IU/kg (57.3, 57.3)	N/A
GU – 1 procedure				
Number of procedures managed with additional prophylactic factor concentrate (%)	0	0	0	0
Median prophylactic cumulative dose/surgery (Q1, Q3)	N/A	N/A	N/A	N/A
Number of procedures associated with treatment for postoperative bleeds (%)	0	0	0	0
Median cumulative postoperative dose/surgery (Q1, Q3)	N/A	N/A	N/A	N/A
Other – 1 procedure				
Number of procedures managed with additional prophylactic factor concentrate (%)	0	0	0	0
Median prophylactic cumulative dose/surgery (Q1, Q3)	N/A	N/A	N/A	N/A
Number of procedures associated with treatment for postoperative bleeds (%)	1 (100)	0	0	0
Median cumulative postoperative dose/surgery (Q1, Q3)	81.0 µg/kg (81.0, 81.0)	N/A	N/A	N/A

Table 3. Outcomes of minor surgeries in participants without FVIII inhibitors

	Non-inhibitor (n=45)		
	SHL FVIII	EHL FVIII	Other haemostatic agent*
CVAD – 15 procedures			
Number of procedures managed with additional prophylactic factor concentrate (%)	4 (26.7)	1 (6.7)	0
Median prophylactic cumulative dose/surgery (Q1, Q3)	58.3 IU/kg (46.2, 62.5)	45.7 IU/kg (45.7, 45.7)	N/A
Number of procedures associated with treatment for postoperative bleeds (%)	2 (13.3)	1 (6.7)	0
Median cumulative postoperative dose/surgery (Q1, Q3)	77.4 IU/kg (62.5, 92.3)	45.7 IU/kg (45.7, 45.7)	N/A
Dental – 27 procedures			
Number of procedures managed with additional prophylactic factor concentrate (%)	10 (37.0)	1 (3.7)	2 (7.4)
Median prophylactic cumulative dose/surgery (Q1, Q3)	46.8 IU/kg (36.2, 50.2)	25.5 IU/kg (25.5, 25.5)	N/A
Number of procedures associated with treatment for postoperative bleeds (%)	7 (25.9)	0	1 (3.7)
Median cumulative postoperative dose/surgery (Q1, Q3)	53.2 IU/kg (49.6, 129.0)	N/A	N/A
GI – 11 procedures			
Number of procedures managed with additional prophylactic factor concentrate (%)	4 (36.4)	1 (9.1)	1 (9.1)
Median prophylactic cumulative dose/surgery (Q1, Q3)	40.1 IU/kg (40.1, 49.7)	52.9 IU/kg (52.9, 52.9)	N/A
Number of procedures associated with treatment for postoperative bleeds (%)	1 (9.1)	0	1 (9.1)
Median cumulative postoperative dose/surgery (Q1, Q3)	†	N/A	N/A
Other – 6 procedures			
Number of procedures managed with additional prophylactic factor concentrate (%)	2 (33.3)	2 (33.3)	1 (16.7)
Median prophylactic cumulative dose/surgery (Q1, Q3)	37.1 IU/kg (34.3, 40.0)	64.9 IU/kg (40.7, 89.2)	N/A
Number of procedures associated with treatment for postoperative bleeds (%)	2 (33.3)	0	2 (33.3)
Median cumulative postoperative dose/surgery (Q1, Q3)	78.0 IU/kg (40.0, 116.0)	N/A	N/A

N values indicate numbers of participants within each population.
*Includes aminocaproic acid, tranexamic acid and desmopressin; †Data not available. CVAD, central venous access device; EHL, extended half-life; ENT, ear nose and throat; GI, gastrointestinal; GU, genitourinary; IQR, interquartile range; N/A, not applicable; pd, plasma-derived.

Conclusions

- This analysis features the largest report of surgery data for PwHA receiving emicizumab in the US.
- The majority of procedures were not associated with treated bleeds, consistent with previously published surgeries data from the HAVEN 1–4 studies.[1]
- Data from this analysis may inform the development of guidelines for the surgical management of PwHA in the future.

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