Reporting of Administration Site Reactions with Parenteral Drugs for the On-Demand Treatment of Hereditary Angioedema Attacks – Analysis of the FAERS Database 2009 to 2022

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Background

- Hereditary angioedema (HAE) is a rare genetic disease associated with recurrent and unpredictable episodic attacks of tissue swelling, which may be life-threatening if involving the airway
- Treatment guidelines recommend that patients should have access to on-demand therapy to treat attacks as early as possible to reduce the severity and duration of the attack[1-3]
  - Currently available on-demand treatments for HAE attacks are administered subcutaneously or intravenously[3]
- The most common adverse events reported in clinical trials and post-marketing reports for most of the on-demand drugs are associated with administration site reactions, which range from 3% to 97% of patients[4-6]
  - Few studies have examined the real-world burden of administration site reactions with parenteral on-demand treatments
- The current real-world study was driven by two objectives: first, to describe reported rates of all administration site adverse drug reactions (ADRs) for approved on-demand HAE therapies using the FDA's Adverse Event Reporting System (FAERS); and second, to detect administration site ADRs for approved on-demand HAE therapies with higher-than-expected reporting rates compared to other non-HAE parenteral drugs in the FDA registry

Methods

Data Source

- We searched FAERS data from 10/1/2009 to 3/31/2022 for human C1 inhibitor (pdC1-INH), ecallantide, icatibant, and recombinant C1 inhibitor (rhC1-INH)
  - The FAERS database contains information on adverse event and medication error reports submitted to FDA by healthcare professionals (such as physicians, pharmacists, nurses, and others) and consumers (such as patients, family members, lawyers, and others)
- Cases were only included if the HAE drug was listed as the 'primary suspect' potentially leading to an administration site ADR

Variable Creation

- For the first objective, to describe the reported rates of all administration site ADRs, the ADR preferred terms from the Medical Dictionary for Regulatory Activities Preferred Terms (MedDRA) were grouped into an ADR domain based on semantic and/or clinical similarity
  - This process resulted in 18 overarching ADR domains (**Table 1**). For each drug and ADR domain, the number of reports was calculated per year from the time of the US approval through 3/31/2022
- For the second objective, only the preferred terms associated with injection site ADRs identified from clinical trials and denoted on approved HAE drug US package inserts were included (**Table 2**)
  - An FDA report with at least one of the preferred terms in the composite was flagged as an ADR in this analysis
- For each drug-event pair, the reporting odds ratio (ROR) and the empirical Bayesian geometric mean (EBGM) were calculated to detect drug-ADR pairs with higher-than-expected reporting rates compared to all other drugs with the same route of administration in the FDA registry
  - ROR estimates with a two-sided lower 95% confidence bound >1.0 were considered significant
  - One-sided 95% lower confidence bound of the EBGM was generated, with values >1 considered significant.
  - When both RORs and EBGM values were ≥1, but not both significant, it was reported as an indication of a trend toward higher-than-expected reporting rates, and a strong signal of a disproportionately high event rate for a drug-event pair was declared when both the ROR and EBGM were significant[7]

Table 1. ADR domains

Administration Site ADR Domain	Administration Site ADR
Incorrect Route of Product Administration	Incorrect route of product administration
Poor Venous Access	Poor venous access
Site Pain	Infusion site pain Injection site pain Administration site pain Application site pain Instillation site pain Vessel puncture site pain
Site Bruising	Injection site bruising Administration site bruise Infusion site bruising Catheter site bruise Vessel puncture site bruise
Site Erythema	Infusion site erythema Injection site erythema Catheter site erythema Application site erythema
Site Swelling	Injection site swelling Infusion site swelling Injection site edema Local swelling Application site swelling Vascular access site swelling Catheter site swelling
Site Extravasation	Infusion site extravasation Injection site extravasation Catheter site extravasation
Site Rash	Infusion site rash Catheter site rash Injection site rash Application site rash
Site Related Reaction	Infusion related reaction Injection related reaction Injection site reaction Infusion site reaction
Site Hemorrhage	Infusion site hemorrhage Incision site hemorrhage Injection site hemorrhage Medical device site hemorrhage Application site hemorrhage Catheter site hemorrhage Vascular access site hemorrhage
Site Mass	Infusion site mass Injection site mass
Site Nodule	Infusion site nodule Injection site nodule
Site Infection	Injection site infection Vascular access site infection Catheter site infection Infusion site infection Medical device site infection
Site Vesicles	Injection site vesicles Application site vesicles
Site Warmth	Injection site warmth Application site warmth
Site Pruritus	Injection site pruritus Application site pruritus Infusion site pruritus
Site Urticaria	Injection site urticaria Infusion site urticaria
Access Site Complication/Malfunction	Vascular access complication Vascular access site complication Vascular access malfunction

Table 2. ADR composites and associated preferred terms

Composite	Preferred Terms
Administration Site Reactions	Injection site reactions Injection site pain Injection site redness Injection site pruritus Injection site irritation Injection site urticaria Injection site bruising Injection site hematoma Injection site hypoesthesia Injection site edema Injection site swelling Injection site warmth Injection site burning Injection site numbness Injection site pressure sensation

Results

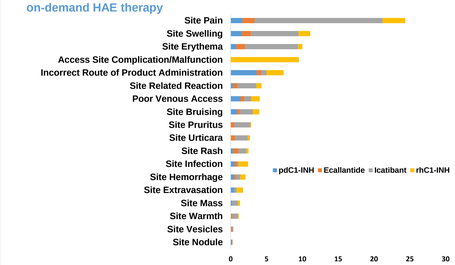
Table 3. Annual reports of administration site reactions

	pdC1-INH (Oct 12, 2009)		Ecallantide (Dec 1, 2009)		Icatibant (Aug 25, 2011)		rhC1-INH (July 16, 2014)	
Year	N reports	Annual total	N reports	Annual total	N reports	Annual total	N reports	Annual total
1	15	0	23	0	43	1	13	0
2	60	0	45	1	87	2	267	0
3	203	0	200	4	535	70	243	3
4	150	0	275	2	392	14	738	5
5	267	0	506	12	618	21	942	2
6	289	0	792	6	389	21	1083	4
7	592	1	994	10	469	15	926	4
8	653	2	54	2	599	26	784	1
9	363	0	60	0	508	25		
10	731	5	32	0	2396	43		
11	944	11	67	2	640	14		
12	305	2	81	2				
13*	214	1	16	0				

*Year 13 is partial through end of Q12022

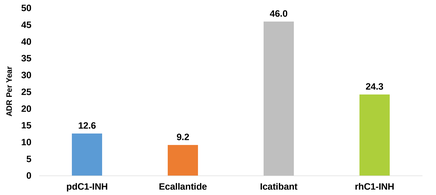
- During the first 2 years of commercial availability, there were very few reports of administration site ADRs across drugs with the exception of rhC1-INH (**Table 3**)
- The number of reports increased considerably at year 3 and generally increased over time after year 3
- Female patients reported most of the reported administration site ADRs, with similar proportions of females across therapies (76% to 83%)
  - PdC1-INH had the highest proportion of reports by males (23%), while ecallantide (11%) and icatibant (14%) had a similar proportion of reports by male patients
    - No reports were by males who were using rhC1-INH
- The average age of HAE patients who reported administration site ADRs was similar across therapies (mean [SD], pdC1-INH, 42.9 [18.7]; icatibant, 42.3 [15.3]; rhC1-INH, 43.5 [9.4]), with the mean age of patients using ecallantide being nominally lower (37.5; [17.4])
  - The age distribution was much narrower for rhC1-INH (SD=9.4) compared to the other three drugs, with standard deviations ranging from 15.3-18.7

Figure 1. Specific administration site ADRs per year by FDA-approved parenteral on-demand HAE therapy



- The five most frequently reported administration site ADR domains included injection site pain, site swelling, site erythema, access site complications/malfunctions, and incorrect route of product administration (**Figure 1**)
  - Access site complications/malfunctions were only reported for rhC1-INH with 9.5 reports per year
- Icatibant had the highest reported rate of administration site ADRs per year for site pain (17.9 per year), site swelling (6.7 per year), and site erythema (7.4 per year). PdC1-INH had the highest rate of incorrect route of product administration at 3.7 per year

Figure 2. Total administration site ADRs per year by FDA-approved parenteral on-demand HAE therapy



- **Figure 2** provides the total number of ADRs per year for each of the four on-demand HAE therapies
  - Icatibant had the most administration site ADRs reported per year with 46, rhC1-INH had 24.3 ADRs reported per year, while pdC1-INH and ecallantide had a similar amount of ADRs reported per year (12.6 vs 9.2, respectively)

Table 4. Reporting odds ratio and empirical Bayesian geometric mean values for HAE on-demand parenteral drugs

HAE Drug (FDA approval)	Adverse Drug Reaction	N of 'Primary suspect' cases	ROR (95% CI)	EBGM (95% CI Lower Bound)
pdC1-INH (Oct 12, 2009)	Administration site reactions composite (vs other IV)[a]	22	3.59 (2.36-5.46)	1.97 (1.39)
Ecallantide (Dec 1, 2009)	Administration site reactions composite (vs other SC)	41	0.39 (0.28-0.53)	0.38 (0.29)
Icatibant (Aug 25, 2011)	Administration site reactions composite (vs other SC)[b]	252	1.15 (1.01-1.30)	1.00 (0.90)
rhC1-INH (July 16, 2014)	Administration site reactions composite (vs other IV)[b]	19	2.85 (1.82-4.48)	1.32 (0.90)

CI confidence interval, ROR reporting odds ratio, EBGM empirical Bayesian geometric mean, IV intravenous, SC subcutaneous
[a]Both ROR and EBGM lower-bound CI values were >1; [b]ROR or EBGM lower-bound CI values >1

- The results of the predictive analysis examining the reporting rate of administration site reactions for each HAE drug are provided in **Table 4**
  - PdC1-INH showed a statistically significant elevated reporting rate of injection site reactions (ROR=3.59 [2.36-5.46]; EBGM=1.97 [1.39])
  - A statistical trend toward increased reporting rate of injection site reactions was found for icatibant (ROR=1.15 [1.01-1.30]; EBGM=1.00 [0.90])
  - Similarly, rhC1-INH showed a statistical trend toward increased reporting rate of injection site reactions (ROR=2.85 [1.82-4.48]; EBGM=1.32 [0.90])

Discussion

- Except for rhC1-INH, the raw annual reporting rates of administration site reactions in the FAERS database were low during the first 2 years each drug was commercially available; for all drugs, the reporting rates increased over time (**Table 3**)
  - This finding runs counter to previous work suggesting that reporting rates are highest rates typically in the first 2 years of commercial availability[8]
- Reported yearly rates of administration site reactions were greatest for icatibant, especially for injection site pain (**Figure 1 and 2**)
  - This finding is not surprising given that the most common adverse effects in the pivotal FAST-1 and FAST-2 trials were injection-site reactions, which were experienced by most patients receiving icatibant in both trials (26 [96%] and 35 [97%], respectively)[9,10]
- Ecallantide had one of the lowest number of reported rates per year of administration site ADR in the current study, which mirrors the integrated analysis of the pivotal EDEMA3 and EDEMA4 clinical trials that found only 3% of patients reporting injection-site reactions[4]
- The results from the ROR and EBGM analyses indicated that administration site ADRs listed on the label of pdC1-INH were high when compared with other drugs utilizing the same administration route (**Table 3**)

Limitations

- It should be noted that due to the nature of the FAERS registry, there are several limitations:
  - Administration site ADRs are not exposure-adjusted and are based on spontaneous reporting; thus, they cannot be used to estimate incidence
  - Reporting rates may differ among the included drugs
  - Reporting rates may vary over time, with the highest rates typically in the first 2 years of commercial availability[8]
- Adverse events are significantly underreported in spontaneous reporting systems such as FAERS[11]
  - A number of previous studies suggest that underreporting may be driven by health care providers' lack of knowledge of, or apathetic attitudes about, ADR reporting[12-14]

Conclusions

- FAERS real-world data suggest that patients experience a treatment related burden due to administration site ADRs from the use of currently approved parenteral on-demand therapies for HAE attacks
  - The current results are likely underestimating the real-world burden due to administration site ADRs
- These findings support the conclusions from the FDA Patient Voice Summit where patients stressed the difficulties surrounding parenteral administration and their desire for less invasive routes of administration[15]
- Evidence from patient-reported experiences, safety reports from clinical trials and post-marketing studies, and the real-world results presented here suggest that alternatives to on-demand therapies administered parenterally would reduce administration related burden to patients with HAE

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