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Real-World Treatment Burden Associated with Parenteral On-Demand Therapies for Hereditary Angioedema

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Background

- Hereditary angioedema (HAE) is a rare genetic disease associated with unpredictable episodic attacks of tissue swelling which may be life-threatening if involving the airway[1]
- HAE treatment guidelines recommend patients always have access to on-demand therapy to treat attacks as early as possible[1]
- Currently available on-demand treatments for HAE are administered subcutaneously or intravenously[1]
- Patients with other chronic diseases (e.g., diabetes, asthma) have reported that the treatment burden associated with injections was often a barrier to treatment[2,3]
- While previous studies have shown that prophylactic parenteral HAE therapies are associated with significant administration site discomfort and burden,[4,5] few studies have examined the real-world burden associated with parenteral on-demand treatments
- The objective of this analysis was to describe reported administration site adverse drug reactions (ADRs) for approved on-demand HAE therapies using the FDA's Adverse Event Reporting System (FAERS)

Methods

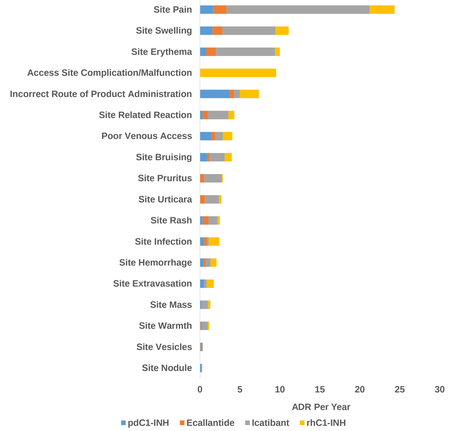
- FAERS contains information on spontaneous adverse event and medication error reports submitted to the FDA by healthcare professionals and the public
- The FAERS database was searched (10/01/2009 to 03/31/2022) for reports of all FDA-approved on-demand therapies for HAE attacks which included human C1-inhibitor (pdC1-INH), ecallantide, icatibant, and recombinant C1-inhibitor (rhC1-INH)
- The number of administration site ADRs, where the drug was listed as "primary suspect" were recorded for each drug
- ADR preferred terms were then 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 were calculated per year from the time of their approval through 03/31/2022
- Descriptive results are presented

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

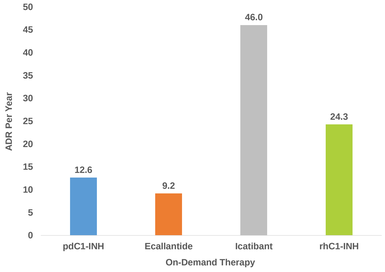
Results

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



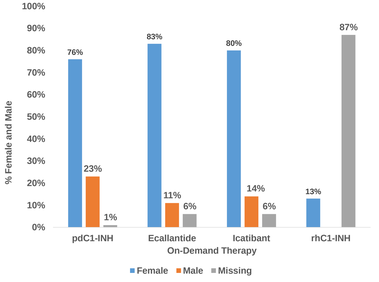
- The five most frequently reported administration site ADR domains included injection site pain, site swelling, site erythema, access site complications/malfunctions, and incorrect route of product administration (**Figure 1**)
- Icatibant had the highest reported rate of administration site ADRs per year for site pain (17.9 per year), site swelling (6.7 per year), and site erythema (7.4 per year) (**Figure 1**)
- rhC1-INH was the only drug for which access site complications/malfunctions (9.5 per year) were reported (**Figure 1**)
- For pdC1-INH and ecallantide, rates for many of the ADRs were under 2 (**Figure 1**)
- Icatibant had the most administration site ADRs reported per year followed by rhC1-INH (**Figure 2**)

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



- Mean ages of HAE patients who reported administration site ADRs were similar for pdC1-INH, icatibant, and rhC1-INH (42.3-43.5 years), although the mean patient age for ecallantide reports was slightly lower (37.5 years)

Figure 3. Sex distribution by FDA-approved parenteral on-demand HAE therapy



- The majority of the reported administration site ADRs were made by female patients (**Figure 3**)

Discussion

- Although adverse events are underreported in spontaneous reporting systems (reporting estimated to represent just 6% of actual events),[6] data mining of such databases may reveal clinically important associations to help guide clinical decision-making[7]
- ADR results are generally consistent with those found in clinical trials and FDA-approved labels, including icatibant, for which 97% of patients experienced administration site reactions[8]
  - Ecallantide had one of the lowest administration site ADR reports; this mirrors clinical trials, which found only 3% of patients reporting injection-site reactions[9]
- Although there are no differences in prevalence of HAE due to sex,[10,11] the majority of injection-site ADRs were reported by females
  - Women are more affected by intensity and frequency of HAE attacks than men[12,13]
  - Women are more likely to report ADRs than men regardless of condition[14]

Limitations

- While the results of this study are compelling, it should be noted that due to the nature of the FAERS registry, there are a number of limitations:
  - Administration site ADR rates are not exposure-adjusted and are based on spontaneous reporting and, thus, cannot be used to estimate incidence
  - Reporting rates may not be similar across included drugs
  - Reporting rates may vary over time with the highest reporting rates typically in the first two years of commercial availability[7]

Conclusions

- FAERS real-world data suggest that patients experience substantial burden due to administration site ADRs from the use of currently approved parenteral on-demand therapies for HAE attacks
- On-demand treatments that have less traumatic routes of administration remain an important unmet need

Acknowledgments

The authors wish to thank Jason Allaire, PhD of Generativity Health Outcomes Research for his assistance with this poster. Funding for Dr. Allaire was provided by KalVista Pharmaceuticals.

Disclosures

Raffi Tachdjian discloses the following relationships with KalVista Pharmaceuticals (honoraria for advisory work), Takeda (honoraria for research, speaking, and advisory work), CSL Behring (honoraria for research, speaking, and advisory work), Pharming (honoraria for speaking and advisory work), Biocryst (honoraria for research, speaking and advisory work), Pharvaris (research grant). Sinisa Savic discloses the following relationships with KalVista Pharmaceuticals (honoraria for expenses and advisory work), CSL Behring (honoraria for expenses, advisory work, and research), Novartis (honoraria for expenses, advisory work, and research), and Biocryst (honoraria for advisory work).Moshe Fridman reports receiving consulting fee from KalVista Pharmaceuticals. Joao Frade, Paul K. Audhya and Marie Fasehun are employees and own stock in KalVista Pharmaceuticals.

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