Poster #25

An analysis of fatalities in persons with congenital hemophilia A reported in the FDA Adverse Event Reporting System (FAERS) database

Christian De Ford,[1] Peter Kuebler,[2] Aijing Shang,[1]
Richard H. Ko,[2] Tiffany Chang,[2] Fabián Sanabria[1]

Summary

Fatalities in persons with congenital hemophilia A (PwCHA) can be reported to the US Food and Drug Administration Adverse Event Reporting System (FAERS) database.

FAERS was searched for fatalities reported between January 1, 2000 and March 31, 2020 in people receiving coagulation products, namely factor VIII (FVIII), bypassing agents, and emicizumab.

A total of 749 fatalities in people receiving coagulation products were reported; **519** were in PwCHA, or those receiving coagulation product for an unknown condition.

Hemorrhage 22.2%

Regardless of the coagulation product used, the most common cause of fatality in this population was hemorrhage.

Receive a copy of this poster https://bit.ly/3irMwdP

Find other presentations of trials sponsored/supported by Roche https://medically.gene.com/global/en/Haematology/Congresses/nhf-2020.html

[1]*F. Hoffmann-La Roche Ltd, Basel, Switzerland;*
[2]*Genentech, Inc., South San Francisco, CA, USA*

Introduction

- Disease- and treatment-associated mortality is of great interest to the hemophilia community.
  - This is especially true for newly available therapies.
- The FAERS database catalogs adverse events (AEs), including fatalities, for all US Food and Drug Administration (FDA)-approved drugs.
  - Reports are received from around the world, including from industry, healthcare providers, patients and caregivers, among others.
- Here we summarize causes of fatality in PwCHA treated with FDA-approved coagulation products as reported to FAERS in the last 20 years.
  - We also compare the reported causes of fatality across conventional therapies and the bispecific antibody emicizumab.

Methods

The FAERS dashboard was searched for all AEs associated with FDA-approved coagulation product use between January 1, 2000 and March 31, 2020.

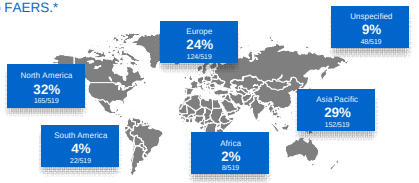
- The coagulation products that were searched included:
  - **FVIII** – plasma-derived and recombinant; standard and extended half-life.
  - **Bypassing agents** – activated prothrombin complex concentrate (aPCC), recombinant activated FVII (rFVIIa).
  - **Emicizumab**.
- The 'outcome' column was filtered to show cases labeled as 'died' only.
- Cases assessed to be duplicates were removed.
- Where individuals were exposed to multiple coagulation therapies at the time of death, the first therapy reported was used for classification.
- Using a framework for assessing mortality,[1] each case was categorized per common causes of fatality in the hemophilia A (HA) and non-HA populations.[2]

Results

Overall, 749 fatalities alongside coagulation product use were identified: 422 in PwcHA, 230 in acquired HA (AHA), and 97 in unknown conditions.

- Excluding AHA, **519** fatalities were reported worldwide in the last 20 years (**Figure 1**).

Figure 1. Geographical distribution of fatal cases (*N* = 519) reported to FAERS.*

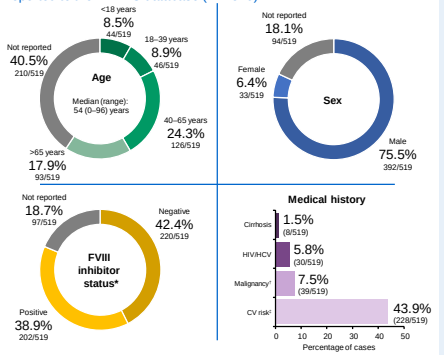


*Fatal cases contemporaneous to coagulation product use reported to FAERS between January 1, 2000 and March 31, 2020.

The median age at time of death was 54 years, and a large proportion of cases were reported with cardiovascular risk factors (Figure 2).

- In total, 16 fatalities (16/519, 3.1%) were reported in infants aged 0–2 years.

Figure 2. Demographics and clinical characteristics of fatalities in PwcHA or those receiving coagulation product for an unknown condition reported to the FAERS database (*N* = 519).

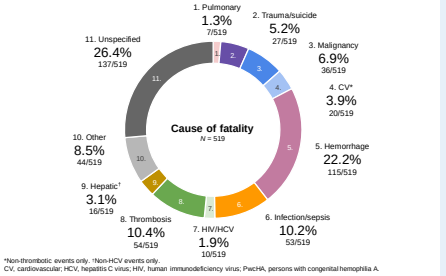


Note: these data are not exhaustive as they are extracted from spontaneous reports provided to FAERS. *Assumes that those individuals receiving bypassing agents, as indicated in their FAERS case report, were FVIII inhibitor positive and that those receiving FVIII products were FVIII inhibitor negative. †Current or historic. ‡Individual with ≥1 CV risk factor. Not all cases have sufficient information to extract CV risk factors. Factors considered to be associated with CV risk include age, hypertension, diabetes, and hyperlipidemia. Presence of CV risk factors was also established from assessment of reported medications.
CV, cardiovascular; FVIII, factor VIII; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PwcHA, persons with congenital hemophilia A.

When applied to a mortality framework,[1] the most common (22.2%, 115/519) cause of fatality across all products was hemorrhage (Figure 3).

- Fatalities from infection/sepsis (10.2%), malignancy (6.9%), and cardiac dysfunction (non-thrombotic, 3.9%) were reported for all coagulation products.
- Fatalities associated with human immunodeficiency virus/hepatitis C virus (1.9%) were only reported in persons taking FVIII.
- Over a quarter (26.4%) of fatalities reported did not specify a cause of fatality.

Figure 3. Causes of fatality in PwcHA or those receiving coagulation product for an unknown condition reported to the FAERS database.

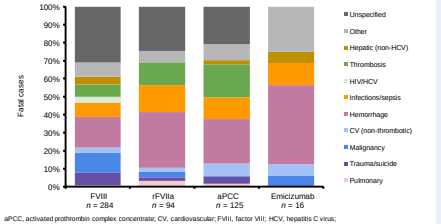


*Non-thrombotic events only. †Non-HCV events only.
CV, cardiovascular; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PwcHA, persons with congenital hemophilia A.

The causes of fatalities reported alongside emicizumab use (*n* = 16) are not inconsistent with those reported with other coagulation products (Figure 4).

- While data in FAERS is not comprehensive for any product, emicizumab is the only product with no fatalities reported to FAERS attributed to thrombosis (including myocardial infarction and stroke).
- Due to a shorter time on market, emicizumab has far fewer cases than conventional therapies. Additionally, FAERS does not comprehensively list all cases due to reporting requirements, and a delay between reporting and publication.

Figure 4. Causes of fatality in PwcHA or those receiving coagulation product for an unknown condition reported to the FAERS database by coagulation product (*N* = 519).

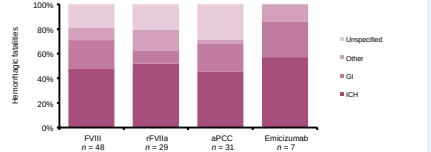


aPCC, activated prothrombin complex concentrate; CV, cardiovascular; FVIII, factor VIII; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PwcHA, persons with congenital hemophilia A; rFVIIa, recombinant activated FVII.

Around half (48.7%, 56/115) of all hemorrhagic fatalities were reported as intracranial hemorrhage (ICH), a rare but life-threatening complication of HA[3] (Figure 5).

- The proportion of ICH fatalities was consistent across coagulation products.

Figure 5. Subcategorization of hemorrhagic fatalities in PwcHA reported to the FAERS database.



aPCC, activated prothrombin complex concentrate; FVIII, factor VIII; GI, gastrointestinal; ICH, intracranial hemorrhage; PwcHA, persons with congenital hemophilia A; rFVIIa, recombinant activated FVII.

Conclusions

- Causes of mortality in persons with congenital hemophilia A are generally consistent across coagulation products.
- Underreporting, variability in reporting, limited case information, missing data, and small overall numbers in the FAERS database hamper classification of cases.
- Improved reporting of adverse events, including fatalities, would enable better evaluation of mortality risk in persons with congenital hemophilia A.

Presented at the National Hemophilia Foundation (NHF) Bleeding Disorders Virtual Conference | August 1–8, 2020

References

1. Pipe SW, et al. Presented at NHF 2020; poster #23;
2. Hay CRM, et al. Presented at NHF 2020; poster #32;
3. Mahajerin A, et al. Presented at ASH 2019; poster P-2398.

Acknowledgments

Third-party medical writing support for this poster was provided by Sophie Nobes, BSc, of Gardiner-Caldwell Communications and was funded by F. Hoffmann-La Roche Ltd.

Disclosures

CDF: Employee of and holder of stocks in F. Hoffmann-La Roche Ltd.; **PK:** Employee of and holder of stocks in Genentech, Inc.; **AS:** Employee of, holder of stocks in, and receipt of expenses from F. Hoffmann-La Roche Ltd.; **RHK:** Employee of and holder of stocks in Genentech, Inc.; **TC:** Employee of and holder of stocks in Genentech, Inc.; **FS:** Employee of and holder of stocks in F. Hoffmann-La Roche Ltd.