Poster #23

A contemporary framework for understanding mortality in people with congenital hemophilia A (PwcHA)

Steven W. Pipe,[1] Rebecca Kruse-Jarres,[2] Johnny N. Mahlangu,[3] Glenn F. Pierce,[4] Flora Peyvandi,[5] Fabian Sanabria,[6] Peter Kuebler,[7] Richard H. Ko,[7] Tiffany Chang,[7] Charles R.M. Hay[8]

Summary

The hemophilia treatment landscape is rapidly evolving.

Newer therapies offer the potential of improved efficacy and decreased treatment burden;[1–4] however, experience with newer agents is limited and their safety profiles are variable and less known in the real world.[5]

We identified a need for a unified approach for reporting types and causes of death to better understand mortality in persons with congenital hemophilia A (PwcHA).

The framework presented here enables the consistent and objective assessment of fatalities in PwcHA.

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[1]Departments of Pediatrics and Pathology, University of Michigan, Ann Arbor, MI, USA; [2]University of Washington, Seattle, WA, USA and Washington Center for Bleeding Disorders, Bloodworks Northwest, Seattle, WA, USA; [3]University of the Witwatersrand and NHLS, Johannesburg, South Africa; [4]World Federation of Hemophilia, Montreal, Canada; [5]IRCCS Ca' Granda Foundation, Ospedale Maggiore Policlinico, Milan, Italy; [6]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [7]Genentech, Inc., South San Francisco, CA, USA; [8]UK National Haemophilia Database, Manchester, UK and Manchester Royal Infirmary, Manchester, UK

Introduction

- Despite advances in therapies for hemophilia A (HA), PwcHA currently have a shorter life expectancy compared with males in the general population.[6–8]
- The treatment landscape of HA is evolving rapidly and substitution and gene therapies offer the prospect of improved efficacy and decreased treatment burden.[1–4]
  - However, compared with traditional clotting factor concentrates, the safety profiles of newer agents in the real world are limited, and may be different based on their mechanism of action.[5]
  - In addition, safety reports which are published after new agents are approved may lack key contextualizing data, making it difficult to interpret the safety data.
- A consistent approach to reporting fatal events and causes of death is needed to better understand deaths in PwcHA. This will enable better assessments of the risks and benefits of treatments and allow the impact of the treatment on the hemophilia community to be monitored.
- Here we aim to provide a contemporary understanding of causes of death in PwcHA and a framework allowing for the consistent interpretation of fatal events and analyses of mortality trends of past, present, and future hemophilia therapeutics.

Methods

Causes of mortality in both PwcHA and the general population were compiled and grouped as shown in Figure 1.

Figure 1. Methods used to develop the framework for assessing fatalities in PwcHA.

1. Causes of death in PwcHA were compiled from:

A systematic literature review	The US Food and Drug Administration Adverse Event Reporting System (FAERS) database	Expert clinical insights

2. Leading causes of death in the US and worldwide non-hemophilia populations were sourced from:

Centers for Disease Control and Prevention[9]	World Health Organization[10]

3. All causes of death were categorized into:

Hemophilia A-associated deaths	Non-hemophilia A-associated deaths

4. Causes of death were further grouped into subcategories reflecting the leading causes of death in the non-hemophilia population and those most relevant to PwcHA

5. The mortality framework was assembled for assessing fatalities in PwcHA

PwcHA, persons with congenital hemophilia A.

Results

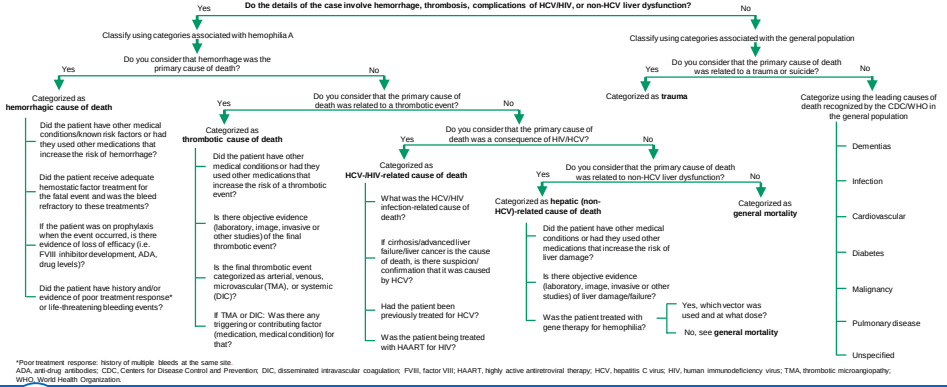
We propose a framework with two main categories: 'HA-associated mortality' and 'non-HA-associated mortality'.

- Based on a systematic literature review[11] and Food and Drug Administration Adverse Event Reporting System (FAERS) database analysis,[12] we found that PwcHA share mortality causes with the non-hemophilia population; they also retain specific causes associated with complications from hemophilia or its associated treatment.
- HA-associated mortality causes can be further grouped into four primary categories: hemorrhage, thrombosis, human immunodeficiency virus-/hepatitis C virus (HCV)-related, and hepatic (non-HCV)-related.
  - There are then further secondary considerations to enable a more in-depth categorization of complicated cases with multiple reported or contributing causes of death.
  - This assessment should be made by the treating physician or healthcare professional, who will have the most in-depth knowledge of each specific case.
- Non-HA-associated mortality causes can first be categorized as traumatic/suicide or non-traumatic/suicide; this allows the user of the framework to easily distinguish between cases which may or may not contribute to meaningful analyses or yield clinical insights relevant to PwcHA.
  - Based on information from the Centers for Disease Control and Prevention[9] and World Health Organization[10] on the leading causes of death in the US and worldwide populations, non-traumatic, non-hemophilia mortality causes can be categorized as: dementias, infection, cardiovascular, diabetes, malignancy, pulmonary disease, and unspecified.
  - Cases in which not enough information is available are classed in the 'unspecified' category.

Based on the HA-related and non-HA-related categories, we propose the following framework for the quick and comprehensive categorization of fatalities in PwcHA (Figure 2).

- Primary considerations determine the main cause of death. Once the user identifies that a given case contains events related to HA or its treatment, an initial categorization is determined.
- Secondary considerations help to determine contributing factors to fatalities in PwcHA; for example, for cases of refractory hemorrhage, medically complex cases where the fatality is attributable to multiple causes, and cases where the loss of efficacy of the hemophilia treatment contributed to the fatal event.

Figure 2. Framework for the categorization of death.



*Poor treatment response: history of multiple bleeds at the same site.
ADA, anti-drug antibodies; CDC, Centers for Disease Control and Prevention; DIC, disseminated intravascular coagulation; FVIII, factor VIII; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HIV, human immunodeficiency virus; TMA, thrombotic microangiopathy; WHO, World Health Organization.

Conclusions

Here we provide a framework for cross-examining mortality in persons with congenital hemophilia A receiving any hemophilia therapy which is expected to enable a new baseline for past, present, and future analyses.

Crucial factors required for a complete assessment of hemophilia A fatalities have been identified and can be used to provide guidance on future reporting of these events.

Importantly, this presents a unique opportunity to document the public health impact of innovation in drug development and may reveal positive impacts of the evolving treatment landscape.

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