Can the use of data derived from different data sources improve regulatory procedures in a rare disease like Hemophilia A?

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Introduction and Objectives

The therapy of Hemophilia A (HA) is currently on the edge of a historical situation with all the upcoming new products upfront. The number of previously untreated patients (PUPs) to be recruited for clinical trials (CTs) might be difficult to meet in an appropriate timeframe. Well-defined registries might be a potential source to improve knowledge on safety of FVIII products.

Main research questions are:

1. Are data available on 50 PUPs for 50 EDs for a single FVIII product, in CTs and PedNet, and how long has it taken to collect this data?
1. To what extent are results from CTs comparable with each other and with data from PedNet?
1. Which requirements of the clinical guideline were already fulfilled in CTs done before 2012 and which information in PedNet can compliment CT data?

Method

The data of the study reports of 7 CTs (data from 2 CT for one product were merged), performed in the frame of MA, was anonymized and consolidated into a confidential database which was established as part of the ABIRISK project and is located in the Paul-Ehrlich-Institut. This database is not public. Anonymized data from 369 previously untreated and minimally treated patients (PUPs and MTPs) of this CTs performed between 1987 and 2009 and data from 633 PUPs documented in the PedNet registry (Fischer et al.) between 2000 and 2015 are compared and put in relation to the requirements of the *Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products*.

References

- European Medicines Agency. Guideline on the Clinical Investigation of Recombinant and Human Plasma-Derived Factor VIII Products. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109692.pdf. Accessed May 30, 2016.
- Gouw et al. Factor VIII products and inhibitor development in severe hemophilia A. N. Engl. J. Med. 368, 231–239 (2013)
- Fischer et al., Prospective observational cohort studies for studying rare diseases: the European PedNet Haemophilia Registry. Haemophilia (2014), 20, e280–e286

Results

1. Are data available on 50 PUPs for 50 EDs for a single FVIII product, in CTs and PedNet, and how long has it taken to collect this data?

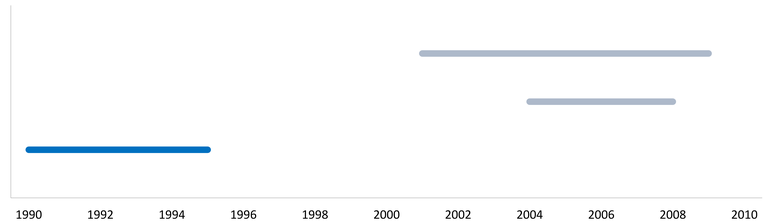

Fig. 1
Time to reach 50 ED in 50 patients for a single FVIII product in **CTs** and **PedNet**

2. To what extent are results from CTs comparable with each other and with data from PedNet

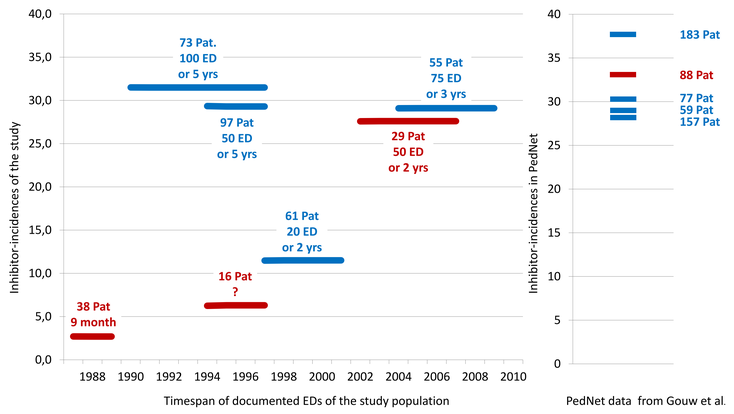

Fig. 2
Red lines: plasma-derived products; **blue lines**: recombinant products

Left: Each line represents one CT. The length of the line illustrates the timespan between the 1st ED of the 1st patient and the last documented ED of all patients of the CT population. The position of the lines represents the inhibitor-incidences. The numbers indicate the number of observed patients and the observational period as defined in the corresponding protocol. Inhibiter test schedules differ not significantly between studies besides in the earliest study were no schedule was defined, but tests were done if a diminished efficacy to FVIII product was observed.

Right: inhibitor-incidences from PedNet data.

3. Which requirements of the clinical guideline were already fulfilled in CTs done before 2012 and which information in PedNet can compliment CT data?

	CTs	PedNet
FVIII consumption	●	●
Physician assessment of response in treatment of major bleeds	●	●
Adverse events	●	●
Central lab	◔	●
Nijmegen method of Bethesda Assay	◔	●
≥ 0,6 BU = low titer, > 5 BU = high titer	◔	●
Inhibitor test at baseline	◔	●
Confirmation measure of a positive test result	◔	●
Inhibitor test if there is suspicion of inhibitor development	◔	●
Inhibitor testing schedule according to GL	◔	●
Vital signs	●	●*

Fig. 3
Requirements of the current clinical guideline are shown and to what extent CTs and PedNet meet these demands.
*Patients in the PedNet centers are directly monitored by the participating doctors, which includes recording data of vital symptoms

Conclusions

The following conclusions could be obtained:

1. Data on 50 PUPs with 50 EDs is only available for 3 products and it has taken between 5 and 9 years to collect this data.
2. The data show that CTs done in PUPs before 2012 are diverse regarding the number of patients enrolled, ED, study period and the time needed to collect data. Moreover, the progress in test conditions makes it difficult to compare the severity of hemophilia and the monitoring of inhibitor development.

   Data in registries can be obtained continuously under the same conditions and parameters which enables the observation of a product over time and allows for comparison of products.
3. Although most of the parameters required by the current clinical guideline were already introduced in early CTs, the observed differences in CT concept and parameters hinders the comparison of study outcome for single products. The PedNet Example shows that key requirements are already fulfilled and applicable for all products.

Our results illustrate that all available information coming from different data sources should be combined to contribute to the knowledge of clinical performance of Hemophilia products to get the best capture of data to support regulatory decisions.

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