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Minimal dataset for post-registration surveillance of new drugs in haemophilia: communication from the SSC of the ISTH

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BACKGROUND AND STRATEGY

The term 'postmarketing surveillance' refers to analyses for the purpose of detecting adverse drug reactions in data accumulated after a medicinal product has been authorized by a regulatory agency [1-3]. The current regulatory process has systematic provisions for obtaining important data needed to ensure the safety of novel drugs almost exclusively during premarketing testing [4]. However, premarketing trials frequently do not have sufficient power to reliably detect important adverse drug reactions [5]. This is because trials are usually powered for the intended therapeutic effect, and therefore they are underpowered for side effects that are rarer than the therapeutic effects. In addition, registration trials are often performed in a relatively healthy subset of patients with the condition of interest, and exclude users of co-medication, thereby reducing the likelihood to detect drug-drug interactions [5]. Therefore, postmarketing surveillance has been introduced to fill this gap by evaluating the safety of medicinal products and to determine unexpected effects occurring after marketing authorization. In the last few years there has been an increasing worldwide emphasis on the development of improved strategies to evaluate the safety of new drugs in the postmarketing phase [6,7] in various fields, including haemophilia.

Since a large number of novel products for haemophilia treatment have recently been or will be licensed soon, such as modified clotting factor concentrates with extended half-life (PEGylated or Fc- or Albumin-fusion products) and alternative haemostatic-enhancing drugs (anti-TFPI, ALN-AT3 or ACE910), we need to have a systematic approach to postmarketing surveillance, in order to monitor their long-term safety.

Therapeutic effects of drugs need to be studied in randomized trials, since physicians will invariably tie prescription of a specific drug to the risk profile of the patient, by factors which usually are too subtle to measure and control for. This confounding by indication may distort the results. For adverse events, usually few risk factors are known and hence confounding is less of a problem, but should still be carefully considered. Since randomized trials are not usually feasible to assess side effects, observational studies are the more suitable to assess safety. However, it should be kept in mind that confounding with incomparability of groups remain the main issues in observational study designs.

Observational studies can either be cohort or case-control studies. The guidelines for cohort studies, see reporting guidelines as STROBE [8], apply for the study of adverse effects, too: an unbiased inception cohort is formed and followed over time. Ideally, all eligible individuals in a well-defined region and time window are included from the time of becoming eligible and are all followed in a similar way. Deviation of this ideal should be considered for its potential to bias, the most important of which is selective inclusion of patients. This results in many registers resembling case series rather than an appropriate baseline sample of a cohort study. The minimum requirement is that participating centres include consecutive patients without selection.

An efficient alternative to cohort studies is to perform case-control studies, which are generally seen as the optimal design to assess adverse drug reactions, since they maximize power and efficiency. In this design, new cases of patients with the complication of interest are included and compared with patients without. A requisite here is an unbiased database of patients with the complication of interest, and an appropriate control group. While maximizing power, drawbacks are that only one type of adverse event can be studied and that only relative rates can be computed, and not absolute risks.

When true registers are built as inception cohorts the two designs can both be employed within the information base along with powerful mixed forms such as nested case-control studies.

Within the framework of the International Society of Thrombosis and Haemostasis, Scientific and Standardization Subcommittee (ISTH/SSC) - Factor VIII, IX and Rare Coagulation Disorders -, a working group was appointed to optimize a minimum standardized set of data necessary to bring information on safety of new drugs after product registration.

The ISTH/SSC working Group consists of physicians, representatives of National and International registries, epidemiologists, representatives of regulatory agencies and of patients organisations (see acknowledgment section).

The members of this working group collaborated to draft a minimal standardised dataset, starting from a critical analysis of the information reported in all available National and International databases/registers (American Thrombosis and Hemostasis Network – ATHN - ; Canadian Hemophilia Surveillance System - CHESS - ; European Haemophilia Safety Surveillance - EUHASS- ; FranceCoag database; PedNet Haemophilia Registry; United Kingdom Haemophilia Centres Doctors' Organisation database – UKHCDO). A preliminary data collection scheme was submitted first to the regulatory agencies, patient associations (World Federation of Hemophilia National Hemophilia Foundation, and European

Haemophilia consortium) and then to pharmaceutical industries for collecting their suggestions and comments. Then, a core set of information to be collected was consolidated as provided in the Supporting Information.

COLLECTION DATASET

The ISTH/SSC working group has developed an essential and user-friendly data format for pharmacovigilance *(Supporting Information).* All haemophilia patients in a participating centre treated for the first time with a new haemostatic product regardless of severity and age, should be registered, including previously untreated (PUPs) and treated patients (PTPs) in order to monitor accurately the onset of any drug-related adverse events.

The electronic data collection forms *(Supporting information)* requires the following information, divided in baseline data at entry, and regularly completed follow-up data:

A. Baseline data

1. Demographic data: patient identifier, data of birth, country, sex, ethnicity, body weight.
2. Clinical data: type of haemophilia, baseline clotting factor activity (% or IU/dl), date of diagnosis, family history of haemophilia, date of the first bleeding, mutation type.
3. Treatment data: each concentrate used, treatment regimen, mean dose per kg per year. For PUPs and for patients switching product, additional questions should be answered in the follow up form.

B. Follow-up data (at least every 6 months or 1 year)

4. Treatment data: details on products and regimens to be provided only for PUPs and for cases undergoing concentrate switches.
5. Adverse events notifications: all adverse events or the absence thereof should be assessed for a long period of time (at least for 3-5 years, preferably for the entire life of patients) including the occurrence of inhibitors, allergic/hypersensitivity reaction, death, malignancy, thromboembolic events (arterial, venous and microangiopathic), and infections or any other unexpected side effect. Considering that in preclinical studies vacuolation in various tissues was observed at high doses after exposure to PEG-conjugated drug [9-11], the introduction of new molecules will need new monitoring methods and as a minimum, renal and hepatic functions should be monitored by an annual sampling of peripheral blood (e.g., creatinine, urea, serum transaminase, alkaline phosphatase, gamma-Glutamyl transferase, pseudocholinesterase, albumin, bilirubin) and urine analysis (e.g. proteinuria, microalbuminuria). Any other type of

unusual or unexpected adverse event (e.g. neurologic disorders or behavioral deficits, liver, kidney, skin) needs to be recorded for any modified products.

6. Inhibitor monitoring: PTPs starting a new product should be followed for at least 100 exposure days (EDs) and assessed at 1, 10-15, 50-75, 100 EDs and then annually, with registration of treatment specific information. PTPs with a past history of an inhibitor will be a particularly important group to observe. Data to be collected and reported for inhibitors developing in PTPs has been described in another statement of this ISTH/SSC [12].

   PUPs should be followed for at least 75 ED and inhibitor testing should be performed at 1, 5, 10, 20, 30, 50, 75 EDs and then annually.

   The assessment of inhibitor development is based on the EMA guideline on the clinical investigation of new FVIII and FIX products [13,14]. A different version was developed for PTPs by the SSC of the ISTH considering the 'biphasic' nature of the inhibitor incidence after FVIII exposure: an early exposure (15, IQR 10–20 EDs) high peak 'epidemic' rate of up to 30% in PUPs is followed by a lifelong low 'endemic' incidence of 0.1–0.6% per patient-year [15].
7. Levels of antibodies against the drug (PEG, Fc, etc) should be reported (when available and tested), including when there is a reduced half-life of the drug, even if there are not standardised assays available until now

DATA STORAGE AND ANALYSIS

The ISTH/SSC working group advises that:

- this system of data collection should be available universally in all Haemophilia Treatment Centres so that every patient treated for the first time with a new haemostatic agent is registered, and all adverse effects including inhibitor development are recorded over time;
- all patients, both PUPs and PTPs should be included;
- the registration of each patient should be recorded at a national level with a unique identifier in order to prevent duplication;
- the unique identified should be implemented also in international databases in order to have a harmonised data collection system;
- data subsets should be shared and analysed at an international level at regular intervals by an independent body.

CONCLUSION

The ISTH/SSC working Group has formulated a consensus essential data collection tool in order to evaluate any potential side effect related to a new haemostatic product in a standardised way to allow cohort and case-control analyses.

This data collection system has the advantages to be uniform and standardised and collects information over extended time periods. It allows pooling of datasets from haemophilia treatment centres around the world in order to detect low frequency adverse effects (not identified in premarketing clinical trials and not detectable in a single cohort) and eventually to link the information to other International databases. This instrument allows also to detect new unlabelled adverse events and unanswered questions of long-term safety observation on novel products in the entire population or specific subgroups of interest [16].

This collection system is a common instrument to share information on safety of the products internationally and implement and exchange the knowledge on novel drugs to ensure a better surveillance for the patients.

This standardised method of data collection will also allow regulators to have access to real life data and identify any unexpected increase in immunogenicity or any unexpected or unknown side effect of a new licensed product.

Addendum

F. Peyvandi wrote the first draft of the manuscript, which was subsequently discussed during conference calls among members of the Project Group and adapted according to the comments of the co-authors in several rounds. All authors provided input for all versions of the manuscript. All authors reviewed and approved the final version of the forms of data collection.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Form of data collection.

Disclosure of Conflict of Interests

F. Peyvandi has received honoraria for participating as a speaker at satellite symposia and educational meetings organized by Ablynx, Bayer, Grifols, Novo Nordisk, and Sobi and she has received consulting fees from Freeline, Kedrion Biopharma, LFB, and Octapharma; she is member of the following scientific advisory boards: Ablynx and F. Hoffmann-La Roche

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