

registries in Europe and worldwide is low, even though the registries are vital in many aspects. The difference of registries vs. epidemiological surveys is often neglected and comparisons between the data not possible. In February 2006, the Western European national member organisations (NMO) Advocacy Initiative (a World Federation of Haemophilia (WFH) – EHC joint activity) considered the lack of national patient registries as number four in the list of threats for patients. The patients' organisations have been active in increasing the awareness of the disease at the political level and in promoting the concept of enhanced cooperation between people with haemophilia, the medical profession and health policy makers.

Discussion and Conclusions

W. Schramm opened the discussion by presenting preliminary data from an annual questionnaire from 1980 to 2005 on inhibitor prevalence in Germany.

The following question was addressed in the discussion of this session:

- *Which benefits would the introduction of a haemophilia patient registry and the link/exchange of data subsets provide?*

Based on the presentations and discussions the following conclusions can be drawn:

There is a clear need for registries. This comprehensive database on factor exposure enables scientific evaluation to optimise the treatment of haemophilia patients and identification of areas for research.

International collaboration will be desirable in this area to increase study power and diversity of products monitored. The starting point could be a network of national registries. Common criteria for data collection are essential to ensure that data are compatible between national registries in order to allow pooling of anonymised data. It was proposed by experts to refer this topic for further consideration by the ISTH SSC Subcommittee on FVIII and FIX, who has already established a working party to develop a consensus minimum international data set for registries.

The main challenges identified were resource issues, compliance issues with the data protection act in the EU, the definition of the data to be collected and combined, and the motivation of the treating physicians to collaborate. Public funding for registries was advocated. All physicians should be encouraged to participate at the national level by explaining the benefits of the registries.

SESSION 7 RISK MANAGEMENT, POST-MARKETING STUDIES AND PHARMACOVIGILANCE FOR FVIII PRODUCTS

The aim of this session chaired by C. Kreft Jais was to present the risk management plan procedure recently introduced in EU and to give the opportunity for the Industry to present its view on pharmacovigilance and risk management aspects for FVIII products.

Presentations

S. Blackburn presented the recent EU guideline on the Risk Management System and explained in which situations applicants should consider a Risk Management Plan. Briefly, the description of the risk management system is submitted in the form of a risk management plan. This plan consists of two parts: (I) the safety specifications and the pharmacovigilance plan; (II) the evaluation of the need for risk minimisation activities and, in addition, a risk minimisation plan, in case of the need for additional (i.e. non-routine) risk minimization activities.

J. Feingold and T. Steinbach presented Wyeth's approach on pharmacovigilance and risk management for FVIII inhibitors. Wyeth clearly advocates the use of registries and recommends a global comprehensive registry with participation of all MAHs, uniform data collection, and standardized laboratory assays.

G. Lemm presented the view of Bayer on clinical trials and post marketing surveillance. It is proposed to include large post-marketing studies with the general objective to evaluate long-term safety and efficacy, and with the specific objective to assess inhibitor risk and perform signal detection on a routine basis with a comprehensive follow-up program.

H. Ehrlich and B. Ewenstein presented Baxter's views on risk management and lessons learnt from registries. A post-marketing surveillance clinical program is considered of utmost importance to contribute to a reliable assessment of inhibitors. Baxter considers that prospective clinical trials in PTPs remain the best indicator of product-related immunogenicity. Baxter considers also that studies in immunologically naive patient populations are confounded by sample size and genetic /non-genetic risk factors. The need of standardisation of key variables (e.g. inhibitor assay, inhibitor definition, duration of observation, immune tolerance treatment methodology) is essential.

F. Bridey presented joint position statements of the International Plasma Fractionation Association (IPFA) members for pre- and post-marketing studies. The importance of defining the best conditions for clinical study design was highlighted to avoid statistical bias, to define the population (severity <1%), to monitor the mode of treatment, and define laboratory parameters. The example of a retrospective study in 104 exhaustive PUPs treated with one plasma-derived FVIII product, a pre-marketing study in PTPs and a post marketing study in PTPs was given.

C. Waller presented the Plasma Protein Therapeutic Association's (PPTA) view on RMP and pharmacovigilance for FVIII products. PPTA member companies do not anticipate any difficulties in implementing the EU guideline on risk management and are committed to work with the authorities on additional approaches for accurate determination of FVIII inhibitor frequencies. PTPs remain the patient population for the investigation of product related immunogenicity and pharmacovigilance is seen as the mainstay of post-licensing risk management. Non-interventional prospective data collection is supported for which a standardised protocol could be implemented in all countries. The FVIII inhibitor assay needs to be further standardised and ideally should be performed in some coordinated laboratories.

Discussion and Conclusions

A risk management plan should be considered for a new product or when a modification to an already approved product is introduced, taking the known genetic and environmental risk factors of inhibitor development into account as well as the severity of this rare serious adverse event.

The pharmacovigilance plan needs to clearly address the assessment of known risks (e.g. risk profile) and its standardized evaluation and the reporting of adverse reactions (ADRs; definition of inhibitors based on laboratory results, clinical signs and recovery and half-life). It needs to be highlighted that every inhibitor detected should be reported in the clinical trial setting and in pharmacovigilance surveillance. In this respect, the role of health care professionals is of utmost importance in order to help health authorities in assessment of pharmacovigilance.

The type I inhibitor is the clinically most dominant inhibitor in haemophilia A and the primary focus of haemophilia treaters. Nevertheless, there should also be alertness for type II inhibitors with their different kinetics. Type II inhibitors were induced under treatment with one modified double-virus inactivated plasma-derived FVIII product (SD + heat treatment at 63°C), which disappeared when patients were taken off the product (see also 5.1).

For a clear observation of rare ADRs, it was reiterated that registries would be an important tool to follow-up patients throughout the life-long course of disease and treatment.

CLOSURE OF OPEN SESSION

B. Ljungberg chaired this part of the meeting, in which the chairpersons from the single sessions gave final remarks.

In conclusion, inhibitor development in PTPs remains the focus of observation for pre-authorisation studies of new and modified recombinant and plasma-derived FVIII products. Standardized protocols for enrolment into the trials as well as for the conduct and evaluation of these studies are needed.

These protocols should contain defined risk factors and be based on ED rather than a specific time period (see previous experience in 5.1).

The need for a risk management plan for FVIII products was clearly identified by all stakeholders in order to enable the detection of inhibitors. The need for registries, large observational studies, and reporting of adverse events are important aspects in the pharmacovigilance setting.

However, from the discussion with the Experts, it was difficult to reach definite conclusions on the recommended design of post-marketing studies and, therefore, this would be further considered by CHMP's Blood Products Working Party and Pharmacovigilance Working Party.

RESTRICTED SESSION ON 2 MARCH 2006,

BPWP MEETINGS IN JUNE AND SEPTEMBER 2006,

RECOMMENDATION FOR THE REVISION OF THE

**NOTES FOR GUIDANCE ON CLINICAL INVESTIGATION OF RECOMBINANT
AND PLASMA-DERIVED FVIII PRODUCTS**

Summary of Restricted Session and BPWP meetings

At the restricted session on 2 March 2006 and the BPWP meetings in June and September 2006, European regulatory experts discussed the views and consensus expressed by experts during the open session on 28 February and 1 March 2006 as follows:

In line with common clinical practice, the diagnosis of a FVIII inhibitor in a haemophilia A patient should primarily be based on clinical observations and be confirmed by FVIII inhibitor testing in the laboratory. The collaboration between clinical and laboratory staff is of most importance. For valid FVIII inhibitor results it is very desirable that also clinical laboratories working under field conditions participate in proficiency studies.

PTPs are defined as patients with more than 150 ED and PUPs as patients with no previous exposure to clotting factors. The suggested categorisation of patients in low-, intermediate- and high-risk groups will be further discussed during the revision of the guidelines on clinical investigation of plasma-derived and recombinant FVIII and FIX products.

From a regulatory point of view, health authorities must obtain sufficient assurance, before granting a marketing authorisation, that a new or modified product does not exhibit excessive immunogenicity. PTPs, who are clinically stable under regular replacement therapy, should be immunotolerant to FVIII, and an enhanced incidence of inhibitors would be unexpected and would be a signal of increased immunogenicity. Therefore for pre-licensing studies, PTPs appear to be the most relevant study population and should remain the target for the pre-marketing clinical studies. Standardised protocols for the enrolment into the trials, for the conduct of the inhibitor assays, especially for the non-interventional studies, and for the evaluation of the trial results are strongly requested.

The need for studying paediatric patients should take into account the Paediatric Regulation. Furthermore, the specific need for paediatric studies for new plasma-derived, new recombinant and modified products (e.g. pegylated) should be considered separately. PUPs are rare patients and BPWP members felt that data in PUPs should be collected when PUPs receive innovative products.

The risk profile is important for the evaluation of data and should be reflected as far as possible by the population studied. For pre-authorisation studies, preferably all known risk factors should be included in the investigation of the product and considered for the evaluation of data, e.g. genetics, age at onset of treatment, immunological situation strongly in correlation with age. According to the current status of scientific knowledge, this should be part of the protocols. For randomized trials there may be the need to match risk factors in study groups. To what extent these aspects may be appropriate for the post-marketing situation, will be further considered during the revision of the guidelines.

With regard to the small haemophilia A patient population, it is considered difficult to obtain firm evidence concerning immunogenicity of a new or modified FVIII product in pre-marketing clinical studies. Moreover, it appears difficult to set a predefined limit for the inhibitor incidence in PTPs solely on the basis of statistical considerations, without knowing the true incidence with plasma-derived and recombinant products on the market.

Considering these points, it is concluded, that the full immunogenicity evaluation of a given product could not be performed in the pre-marketing stage and it is important to foresee particularly efficient mechanisms of monitoring and pharmacovigilance for the post-licensing period. A complete

evaluation of product immunogenicity requires long-term data, which could only be obtained from post-authorisation setting, via post-marketing studies or registries. Post-marketing studies allow requesting of long-term data. An adequate design and standardization of post-marketing studies is of great importance, in order to collect relevant and reliable data to enable proper assumptions on FVIII inhibitor occurrence related to products. All these requirements should be reinforced in the revised guidance. Nevertheless, with an observational design, it will be difficult to stay on one given product, or one type of treatment, over an extended period.

It may not be evident to health care professionals when there has been a change to a specific product on the market through a modification in the manufacturing process. Therefore, in this context, it is of importance that MAHs commit to undertake appropriate inhibitor monitoring also after manufacturing changes. These requirements should be clearly highlighted in a risk management plan.

Also in post-marketing studies, the number of patients will be limited. Therefore, the establishment of national registries with harmonised data sets is strongly supported. In June 2006, as recommended during the expert meeting, CHMP contacted the ISTH SSC Subcommittee on FVIII and FIX products for collaboration on common data sets and also on FVIII inhibitor assay.

BPWP members noted that a new generation of recombinant FVIII products with longer half-life is in development and new experience on FVIII inhibitor development might be gained.

An additional point, which has been raised, concerns the meaningful information on inhibitors, which should be mentioned in the relevant sections of the SPC of a given product. Revision of the core SPC should clearly define what type of data should appear, in order to be as informative as possible for clinicians and patients with regards to the development of inhibitors.

Further Observations and Conclusions, as well as Recommendations for the Revision of the Notes for Guidance and core SPCs

In line with the consensus reached during the open session of the expert meeting, regulatory experts agreed with the following requirements and recommendations for the pre- and post-authorisation monitoring of inhibitor development in haemophilia A patients:

FVIII inhibitor assay

- The Nijmegen modification of the Bethesda assay is recommended for pre-authorisation studies and for post-marketing surveillance. Validated testing should be performed in a centralised laboratory for pre-licensing studies.
- Optimisation of the Nijmegen modification of the Bethesda assay should address the detection of type I, and also type II inhibitors.
- The participation of laboratories involved in clinical studies in proficiency and collaborative studies is essential.
- A threshold of ≥ 0.6 BU for the diagnosis of a low titre inhibitor was defined as well as a titre of ≥ 5 BU for a high titre inhibitor.
- A confirmatory test on a second, separately drawn sample should always be performed in a qualified laboratory. This second sample should be taken prior to any change of treatment and shortly after the previous positive test (within a month).
- For routine inhibitor testing, the inhibitor test should be performed when the plasma FVIII level has reached a pre-substitution nadir rather than at a specific time point. The inhibitor assay should be validated for the impact of residual FVIII on the test results.

Clinical conditions interfering with the FVIII inhibitor assay

- Presence of exogenous or endogenous FVIII: The interference of residual FVIII activity with the FVIII inhibitor assay can be circumvented by heating the sample in a validated step (e.g. one hour pre-treatment at 58°C).
- Lupus anticoagulant (LA): Differentiation of LA from FVIII inhibitors may be crucial, because of the different therapeutic interventions required. Two or more positive test results, particularly from assays with different designs, are more informative and more likely to differentiate LA from anti-FVIII inhibitors.

- **Heparinised ports:** In general, it is recommended for FVIII inhibitor testing to take blood from a vein and not from a port, as flushed heparin has an impact on FVIII inhibitor measurement.
- **Chronic viral infections:** Inhibitors have been detected in patients with chronic viral infections (e.g. HIV, HCV) during anti-viral therapy.

Clinical signs of inhibitor occurrence to be monitored

- **PTP:** Increased bleeding tendency, high consumption, lack of response or efficacy, decreased recovery, shortened half-life are indicative for an inhibitor in PTPs.
- **Infants and young children:** Poor response to treatment, including prophylaxis, is a useful clinical sign of inhibitor occurrence. High titre inhibitors may be indicated by an increased bleeding tendency (e.g. joint bleeds), while treated under a FVIII prophylaxis regimen. Effectiveness of treatment of a fresh joint bleed is measurable. Low titre inhibitors will probably not be detected under FVIII prophylaxis regimens. It is recommended to look at incremental recovery in a sample after infusion. Greatly reduced or no FVIII activity are indicative of an inhibitor. High consumption and increased bleeding are less reliable indicators in infants and young children.
- Careful consideration of all parameters is required, because some inhibitor patients do not bleed.

Clinical relevance of low titre inhibitors

Transient and low titre inhibitors might become a clinically relevant inhibitor in a PTP later in life. This indicates the importance of prolonged follow-up of patients. Such long-term data are much more difficult to collect, but are essential for pharmacovigilance assessment and registries. An additional difficulty in the interpretation of data is that FVIII inhibitor routine testing will often only be carried out in local laboratories rather than a central laboratory.

General recommendation for monitoring inhibitors

- Monitoring of inhibitor development should be started at the onset of treatment with a new or modified product in order to obtain solid baseline data.
- Regular laboratory measurements for inhibitors should be implemented in clinical studies. In addition, clinical signs suggesting inhibitor development should be defined and used to trigger investigations between the regular laboratory visits.
- Routine testing for inhibitors should be carried out on a regular basis. In particular, testing should be frequent in the early stages of replacement therapy. However, frequent sampling may prove difficult in young children.
- In order to identify product-related immunogenicity, all inhibitors should be documented and reported.
- Linking clinical and laboratory findings is very important.

Study population

- Product-related inhibitor development should be studied in PTPs pre-licensing.
- MTPs should not be included together with PUPs.

Definitions

Severe haemophilia A: FVIII baseline level of <1%. For pre-licensing studies, this definition (<1%) should be applied for PTP. In post-licensing studies, also patients with up to 2% baseline level may be included in the protocol for severe haemophilia A, when a separate statistical evaluation for <1% and <2% is provided.

PUP: Patients who never had exposure to clotting products, previous exposure to blood components is not excluded.

PTP: Patients at low risk, e.g. more than 150 ED.

MTP: not clearly defined and not useful concept.

Patient characteristics to be reported

Age

Age at time of first exposure to FVIII

General health status (infections (HIV, Hepatitis and other infections), vaccination)

Reason for treatment (e.g. bleeding, surgery)

Regimens and intensity of treatment (prophylaxis or on demand, in case of surgery continuous infusion or bolus injection, dosages and intervals)

ED (total, and to product under which treatment inhibitor developed)

Genetic risk factors:

Severity of haemophilia A

Gene mutation

Family history of inhibitors

Ethnicity

Mode of treatment

Prophylaxis vs. on demand treatment and continuous infusion

More data should be generated by post-marketing studies and pharmacovigilance reporting on inhibitors, in which information on prophylaxis vs. on demand treatment regimes and continuous infusion are being gathered.

Product switch

For pharmacovigilance reporting, it is important to get information about product switches before and after inhibitor detection. Respective data should be provided. The effects of product switching could also be investigated from registry data. The need for a harmonised data set in order to enable European or international evaluation is emphasized.

Also after changes to a specific product because of modifications in the manufacturing process, appropriate inhibitor monitoring should be undertaken. These requirements should be clearly highlighted in a risk management plan.

Duration and follow-up

Patients should be followed up for at least 50 ED, independently of the exposure period, in clinical studies performed prior to marketing authorisation. Long-term data can be obtained from post-authorisation setting, via post-marketing studies or registries (see below).

Sample size

Considering the small patient population, case control studies in PTPs could be a possible approach to get reliable and relevant data on risk factors for inhibitor incidence. In principle, any inhibitor case seen should be recorded.

Registries

A network of national registries with common criteria for data collection is desirable to ensure that data are compatible between national registries in order to allow pooling of anonymised data. This topic has been referred for further consideration to the ISTH SSC Subcommittee on FVIII and FIX.

Risk management, post-marketing studies and pharmacovigilance for FVIII products

The need for risk management plan, registries, large observational studies, and reporting of adverse events are important aspects in the pharmacovigilance setting for FVIII products.