5.2 DEFINITIONS - PATIENTS CHARACTERISTICS

Session 5.2, chaired by J. Ingerslev, addressed definitions and patients characteristics. Two presentations were followed by a round table discussion, in order to provide consensus statements to the three proposed questions.

Presentations

M. van den Berg presented the re-evaluation of PUP recombinant FVIII studies and the Canal Study. Any diagnosis of inhibitor should be made on clinical findings confirmed with two separately drawn, positive samples. Recovery data and other PK tests were considered necessary for a full diagnosis of inhibitors. Both studies presented by M. van den Berg revealed comparable results indicating that intensive treatment in case of surgery and large bleedings is associated with inhibitor occurrence, while early onset of prophylactic treatment seems to have benefit. Recommendation for further investigation on this potential beneficial effect was proposed.

J. Ingerslev presented, on behalf of J. Oldenburg, a review on risk factors, providing examples of high-risk scenarios for inhibitor development. Two types of risk factors, genetic and environmental, could be considered to determine the risk profile. Predisposing genetic factors are type of FVIII mutation, family history of inhibitors, severity of haemophilia A, race and ethnicity, and polymorphisms and mutations in immune response genes. The environmental factors that may influence the likelihood of inhibitor formation are the age of first exposure to FVIII, immunological challenges, invasive clinical procedures, treatment regimes with FVIII (dosages, intervals); socioeconomic aspects, abnormal FVIII molecules and infant diet.

Discussion and Conclusions

Experts and regulators (J. Astermark, C. Hay, C. Lee, D. Mentzer, W. Schramm, M. van den Berg) participated in the round table discussion:

Three questions were addressed dealing with the definition of severe haemophilia, PUP, MTP and PTP, and the relevant patient characteristics for the evaluation of FVIII inhibitors.

- *Definitions for severe haemophilia A used in different clinical studies vary between FVIII baseline level of < 1% and < 2%. How should severe haemophilia A be defined? The ISTH SSC Subcommittee defined severe haemophilia A with a FVIII baseline level of <1%. Should the SSC classification be adopted in clinical pharmacovigilance studies?*

  Industry representatives pointed out that there is no problem in defining severe haemophilia A as a baseline level <1% for pre-licensing studies. Nevertheless, for post-marketing studies a baseline level of 2% has been chosen in the past in order to meet laboratory difficulties. One industry proposal was to collect all data for FVIII baseline level of < 1% and < 2% in a post-marketing setting, and provide for statistical analysis with distinct results for FVIII baseline level of < 1% and < 2%. Assessment of the gene mutation is recommended whenever possible.

  The final agreement was to adopt the definition for severe haemophilia A of the ISTH SSC Subcommittee, namely a FVIII baseline level of <1%.

- *How should PUP, MTP and PTP be defined on the basis of the total number of exposure days? Is there a value in the introduction of additional categories, e.g. heavily treated PTP? Should the number of exposure days be reported with the product under which the FVIII inhibitor developed?*

  As agreed during the previous session, the categorization of patients as MTPs is not seen as a useful concept. Therefore, the discussion focused on the definitions of PUPs, and PTPs.

  Regarding the definition of PUPs various positions were considered. Agreement was reached that PUPs are patients who have never been exposed to clotting factor products. Nevertheless, previous exposure to other blood components should not be regarded as treatment in this

respect. Agreement was reached that pre-authorisation inhibitor development should be studied in PTPs that are at low risk, e.g. more than 150 ED.

In addition, a different approach to categorise patients in low-risk, intermediate-risk and high-risk groups rather than PUP, MTP and PTP was discussed. The cumulative risk for development of an inhibitor within the first 150 ED is 20-30%. Fifty per cent of those patients that eventually develop inhibitors, develop these within the first 20 ED, 95% within the first 50 ED and >99% within the first 150 ED. It was proposed that patients with more than 150 cumulative ED are grouped as low-risk patients, while patients with less that 20 cumulative ED are regarded as high-risk patients. Nevertheless, for the intermediate risk group, the definition in cumulative ED seems to be more difficult to draw, since patients are still at high risk up to the first 50 ED. The number of ED could be utilised in categorization parameter rather than the classification as PUP or PTP. In terms of pharmacovigilance all patients, including those with moderate and mild haemophilia, should be included in any surveillance.

Regulators needed clear definitions of patients, whatever their basis, number of exposure days, or risk categorization. To provide relevant and reliable data, these definitions should be clearly established and practicable. For pharmacovigilance, it appears important to define categories based on risk, especially for spontaneous reporting. Therefore, further reflection on categorization of patients - low, intermediate and high-risk groups - would be critically considered during the revision of the guidance.

- *Which patient characteristics are relevant for the evaluation of FVIII inhibitors? Is it of value to collect information on ethnicity, type of FVIII gene mutation, general health status, intensity of treatment/consumption, circumstantial factors - e.g. surgery, age at start of first treatment in severe haemophilia A? Are special parameters required for children?*

  The experts agreed that all mentioned patients' characteristics should be recorded: severity of haemophilia A, age, age at time of first exposure to FVIII, race and ethnicity, type of FVIII gene mutation, general health status (infections - HIV, hepatitis and other infections), vaccination, family history of inhibitors, and surgery. Reason for treatment, regimens and intensity of treatment (prophylaxis or on demand, in case of surgery continuous infusion or bolus injection, dosages and intervals), ED (total and on product) should also be recorded.

5.3 MODE OF TREATMENT– CONTINUOUS ADMINISTRATION AND PRODUCT SWITCH

Session 5.3, chaired by J. Ingerslev, addressed the influence of the mode of treatment - continuous administration and product switch – on inhibitor development. Two presentations were given, followed by a round table discussion, in order to provide consensus statements to the three proposed questions.

Presentations

J. van der Bom presented the ideal study design for inhibitors in haemophilia A from an epidemiological point of view. While risk factors for inhibitor development in PUPs (e.g. type of gene mutation, ethnicity) are established, there is little knowledge about the risk factors for inhibitor development in PTPs. Intensity of treatment (continuous infusion, prophylaxis) and switch of product have been investigated as possible risk factors for PTPs. J. van der Bom questioned the feasibility and ethics of a randomised controlled trial to study the occurrence of inhibitor development under continuous infusion in comparison with daily bolus injections due to the high patient number required (2282 PTPs and 96 PUPs). Because of the limited number of haemophilia A patients, case control and cohort studies requiring a smaller sample size are more realistic. Attention should be moved from the determination of incidence to the investigation of risk factors, which cannot be studied in randomized controlled trials. Most knowledge is based on observation and the ideal situation from the epidemiological perspective would be when every patient would carry an electronic logbook for data on treatment and side effects to be entered into a central research data base bi-annually. In addition,

due to the very limited number of patients, it is important for haemophilia treaters to join forces and collaborate across borders.

G. Auerswald presented epidemiology data of inhibitor formation in Bonn and Bremen before 1990 and between January 1990 and July 2001 in patients under immune tolerance therapy (ITT) treated with plasma-derived FVIII concentrates solely and patients treated with recombinant FVIII products. Prior to 1990 the success rate of ITT with plasma-derived FVIII products was 87% (44 /51 cases) at these centres. From 1990 to 2001 the success rate was 82% with plasma-derived high purity FVIII products (23/28 cases) and 43% with recombinant FVIII products (6/14). 13 patients, who failed ITT and were initially treated with highly purified plasma-derived or recombinant FVIII products, were switched to plasma-derived intermediate purity VWF containing products and immune tolerance was achieved in 10 of 13 patients. The inhibitor reappeared in 2 patients after changing back to high purity FVIII product but disappeared under treatment with a VWF-containing intermediate purity plasma-derived FVIII concentrate. In conclusion, FVIII concentrates containing VWF may possess a reduced immunogenic potential.

Discussion and Conclusions

Experts and regulators (G. Auerswald, B. Ljungberg, I. Scharrer, J. van der Bom, M. van den Berg) participated in the round table discussion: Three questions were addressed by the group, dealing with potential impacts of administration practice, continuous infusion and product switch on the development of inhibitors.

- *Does administration practices (like prophylaxis and on-demand treatment) influence the development of inhibitors?*

  The data from the Canal study presented by M. van den Berg in session 5.2 indicated that there is a correlation between prophylaxis / on-demand treatment and the occurrence of FVIII inhibitors: there were significantly less inhibitors in patients under prophylaxis regimen. Some of the participants raised the issue that these results could be confounded by the fact that prophylaxis starts later in life, when a lower risk of inhibitor development exists. In the Canal study, a time dependent analysis was performed in order to take into account this confounding factor.

  Available data in literature seem to support the notion that prophylaxis might be protective with regards to inhibitor development.

  Nevertheless, because a limited amount of data are available on this topic, the respective impacts of on-demand / prophylaxis regimens on the development of FVIII inhibitor need to be further investigated.

- *Does administration by continuous infusion influence the development of inhibitors and is there a need for specific data related to administration by continuous infusion?*

  I. Scharrer started the discussion by reporting on a retrospective trial on inhibitor occurrence after continuous infusion in Germany. Two hundred continuous infusions were performed in 128 patients, of which 14 developed an inhibitor (3 PUPs, 9 PTPs; 5 patients with severe, 1 with moderate and 8 with mild haemophilia). Four of these 14 patients (29%) had a missense mutation, which is striking since J. Oldenburg and colleagues found only 4% missense mutations in more than 100 inhibitor patients. The other 114 patients who did not develop an inhibitor were suffering from severe (78), moderate (8) and mild (8) haemophilia A and from haemophilia B (7). Taken together these data indicate that continuous infusion in patients with mild haemophilia A should be carefully evaluated.

  Participants agreed that there is a need of control data and further investigations to fully answer this question, particularly in mild haemophilia. Participants raised the issue of confounding factors, such as intensity of treatment and ED. The number of ED is lower in patients with mild haemophilia and most of these patients are constantly at risk of developing an inhibitor during high-intensity treatment.

- *The change from one product to another might booster or silence an existing FVIII inhibitor. Currently there is insufficient follow-up on these cases. How should the follow-up after a switch to another recombinant FVIII or plasma-derived FVIII product be standardized?*

  I. Scharrer reported on the review of the risk for inhibitor development in PTPs when switching from plasma-derived to recombinant FVIII. In a series of 5 clinical trials with a total of 307 patients, one patient was found with a de novo, transient low titre inhibitor.

  For pharmacovigilance reporting, it appears important to obtain information about possible product switches before and after inhibitor detection.

  The participants agreed that possible ill effects of product switching could be extracted from registry data. The need for a European or international registry was emphasized.

  Nevertheless, no consensus on whether increased inhibitor testing should be implemented after a product switch was reached. Testing recommendations are different depending on the countries: in United Kingdom, every 6 months is recommended, while in France, after a product switch, inhibitor testing is recommended after 10-20 exposure days, and thereafter according to the patient status: in PTPs, inhibitor testing is performed upon each visit (one or two per year), while in PUPs with severe haemophilia, inhibitor testing is regularly performed every 5-10 until 50 ED, then every 3 months until 100 ED, then every 6-12 months.

5.4 DURATION AND FOLLOW UP, SAMPLE SIZE

Session 5.4, chaired by J. Ingerslev, addressed the duration, follow-up and sample size of clinical studies on inhibitor development. One presentation was followed by a round table discussion.

Presentation

J. Goudemand presented an overview of all available literature data on the scope of the session. While the occurrence of inhibitors is a relatively frequent and early event in PUPs, it is rare in PTPs. Therefore, duration and follow-up in clinical studies should be differently defined for PUPs and PTPs and should be long enough to detect the possible occurrence of inhibitors. In published studies, duration was monitored in exposure days and/or exposure months. Depending on the reasons for use (intensive treatment/ prophylaxis/ on demand), the same number of exposure days was accumulated in very different time periods and it is very likely that the patients were not exposed to the same inhibitor risk. J. Goudemand concluded that in PUP studies, all inhibitor risk factors as well as the exposure days or period of exposure should be documented until at least 50 cumulative ED. In PTPs inhibitor risk factors are probably more therapy-related than patient-related (intensity of previous exposure (>50, > 100, >150 ED), intensity of treatment, prophylaxis, mode of administration, product switch) and should be documented in a defined way. According to current practice in France, Italy and UK, the recommendation for the duration of inhibitor screening is a combination of ED and period of administration. J. Goudemand recommended monitoring clinically relevant inhibitors depending on titre and therapeutic consequences.

Discussion and Conclusions

Experts and regulators (J. Goudemand, C. Lee, R. Seitz, J. van der Bom) participated in the round table discussion. Three questions were addressed dealing with duration, follow-up and sample size required in clinical studies in order to enable proper assumptions on the FVIII inhibitor occurrence.

- *Duration and follow-up are important parameters to compare the FVIII inhibitor incidence in clinical studies. As published in literature, the FVIII inhibitor incidence observed over 2 or 4 years differs. How long should the duration and follow-up period be and how should it be defined, based on exposure days or years? Which clinical and laboratory parameters should be monitored and in which intervals (e.g. prophylaxis, treatment on-demand, consumption, number of bleedings, FVIII plasma level, inhibitor measurement) ?*

The requirements for follow-up of PUPs and PTPs as well as the requirements for pre-authorisation and post-marketing studies should be clearly distinguished.

The risk factors for inhibitor development in PUPs are well understood and experts agreed that PUPs should be monitored for at least 50 ED in clinical trials independently of the exposure period. On the other hand there is limited knowledge about risk factors for inhibitor development in PTPs. Experts suggested a longer follow-up period for PTPs. Considering that patients have the freedom of choice of product and treatment, they should be monitored as long as they are treated with one given product, e.g. through registries.

As previously mentioned in session 5.1, due to the small patient population, it is difficult to obtain firm evidence concerning immunogenicity of a product in pre-marketing clinical studies. According to the current CHMP note for guidance on clinical investigation of plasma-derived and recombinant FVIII products, pre-licensing immunogenicity data should be obtained in 50 PTPs to show that the product under evaluation does not exhibit any signs of abnormal immunogenicity compared to other products on the market. In this context, a follow-up of at least 50 ED seems to be relevant.

On the other hand, post-marketing studies can allow more freedom to request long-term data, notably regarding inhibitor development.

- *Should the number of exposure days to the product under which the FVIII inhibitor developed be given?*

  All the participants agreed to collect the number of exposure days to the product under which the FVIII inhibitor developed.

- *Concerning statistical evidence for a risk of inhibitor formation how should the sample size and observation period in clinical studies be defined to enable proper assumptions on the FVIII inhibitor incidence in PUPs and PTPs?*

  During the meeting, the FDA approach of pre-defining a cut-off for inhibitors was discussed. For the participants, it appears quite difficult to pre-define such a cut-off, based on pre-licensing data, which appear insufficient (see J. van der Bom presentation is Session 5.3). Any inhibitor case seen should be carefully analysed.

  From the presentation of J. van der Bom, it appears that randomised controlled trials to investigate inhibitor incidence are difficult to perform due to the high patient number required. Case control studies in PTPs could be a possible approach in order to get reliable and relevant data on inhibitor risk factors.

SESSION 6 REGISTRIES

Session 6 was chaired by C. Lee. The aim of this session was to discuss experiences gained with patient registries. For this purpose, 5 presentations were given followed by a plenary discussion.

C. Lee opened the session by highlighting the importance of epidemiological data on FVIII inhibitor formation. C. Lee mentioned that excellent data from national registries are already available in some countries. The survey of the existing registries provided by the EMEA was tabled for information. According to the survey, there are national registries in at least 10 Member States and registries are under construction in three Member States. The European paediatric organisation for haemophilia management (PEDNET) also includes a paediatric registry (www.pednet.nl). The International Society on Thrombosis and Haemostasis (ISTH) also has a database for FVIII Deficiency.

Presentations

The question of the potential benefits from introduction of a haemophilia patient registry and the link/exchange of data subsets between registries that could be provided was elaborated in the following presentations.

M. Soucie gave a presentation on the United States Pilot Study of Inhibitors in Haemophilia. The study is based on the Universal Data Collection (UDC) program, which monitors blood safety among recipients of blood products. Even though the UDC is not designed to study inhibitors, some related data are collected including demographics, bleeding frequency, inhibitor test results and all product brands used. In a preliminary study, 2.75 new inhibitor cases per 1000 person years were verified. No robust conclusion on the immunogenicity of different products could be made due to lack of statistical power. M. Soucie explained that, in the pilot post-marketing study, a data coordinator is employed to collect the factor exposure data and ensure the annual blood testing. Methodologies to collect required treatment and bleeding information are being explored. Inhibitor testing is performed in a centralised laboratory. Inhibitor testing is to be done annually and prior to any planned product switch. In addition complete gene sequencing in a central lab is planned. Inhibitor history, infusion logs and product details are collected using specific data collection forms, electronic data entry from the sites and by patient.
M. Soucie mentioned that, when fully implemented this approach will provide the benefits of large population monitoring that yields the most power for studying rare events, permits product choice and avoids random assignment to treatments, and facilitates the quality control of the study. He also elaborated on the need for international collaboration in this field to increase study power and diversity of products monitored.

C. Hay presented the results from the UK National Haemophilia Database (NHD), which was established in 1968. The database collects data to provide national statistics to promote improved healthcare for patients with bleeding disorders. The new diagnoses, deaths and patient demographics are reported. Annual treatment data, including products used, are available from the whole UK. Inhibitors and other adverse events are reported. A vCJD database has been recently developed. The system has a real-time adverse event reporting and quarterly on-line reminders for adverse events. C. Hay showed that the use of recombinant products has been increasing while the use of plasma-derived products has been decreasing from the late nineties. In haemophilia A patients, about 13% have less than 1BU inhibitors, less than 9 % have 1-5 BU inhibitors and only about 1 % have severe haemophilia with more than 5 BU inhibitors. In 1991-2001 28 % of patients changed products. The incidence of inhibitors is highest in the age group from 0 to 9 years of age (22 % in 1990-2003), and decreases remarkably with increasing age (0.5 % in patients aged from 10 to 19 years). The incidence increases again during the fifth and sixth decades. Data on the relative risk by product is not complete and the data between PTPs and PUPs are not directly comparable. The exposure data is available only for younger patients and the risk can be expressed only in terms of treatment years. C. Hay concluded that there seems to be no clear difference between the recombinant products and an improved dataset will be more informative in this regard.

B. Haschberger gave an overview on the building of a national register in Germany. According to the German Transfusion Act, the number of patients with haemophilia, with inhibitors, and the amount of product consumption figures are collected to obtain data concerning the supply situation. Since 1999 the data have been requested in paper questionnaires from the haemophilia treating physicians. The new German register is intended to provide an extended database to enable scientific evaluation to optimise the treatment of the haemophilia patients and to reduce unnecessary exposure and costs. It is also considered important to aggregate international data and harmonise definitions with other national registries. However, several challenges were faced. The German Transfusion Act foresees only the collection of summarised data, but a registry needs individual patient data. Due to the very high impact of data protection in Germany, it was important that the data would be securely anonymised and no list of patients would be generated. The registry will ensure that the data protection mechanism will enable long term follow-up, and diagnostic and therapy data will be included, as well as other extensions like adverse effects and infections. User-friendly software was considered essential for the motivation of the treating physicians. B.Haschberger stated that the German Haemophilia Register, which is planned to start by the end of 2006, is a joint activity of Paul Ehrlich Institute, German Ministry, the German scientific society GTH (Gesellschaft für Thrombose- und Hämostaseforschung), and the patient organisations DHG (Deutsche Hämophilie Gesellschaft) and IGH (Interessengemeinschaft Hämophiler).

H. K. Hartl, chairperson of the European Haemophilia Consortium (EHC) (44 National member organisations) gave the patients' perspective on registries. He pointed out that the number of national