Event Report: EHC Round Table of Stakeholders on 'Clinical Trials in Haemophilia'

About the event

On Tuesday 7 March 2017, the European Haemophilia Consortium (EHC) held a Round Table of Stakeholders at the European Parliament in Brussels, Belgium, to discuss issues in clinical trials for the development of haemophilia treatment.

Over 50 participants attended the event, including patient representatives, healthcare professionals and industry representatives. The event's agenda, list of speakers and presentations can be consulted online on the EHC website. Pictures from the event can be viewed on the EHC Facebook page.

The Round Table was kindly supported by Member of the European Parliament (MEP) Mrs Norica Nicolai (Romania/ ALDE). Dr Miroslav Mikolasik, MEP, also joined and addressed the audience during the event.

On Clinical Trials in Haemophilia

Haemophilia is a rare and congenital bleeding disorder caused by a genetic defect, resulting in a lack of or insufficient coagulation factors VIII or IX in the body. In affected individuals, this causes an inability to clot blood, leading to bleeds in the joints, muscles and soft tissues. If left untreated, this can lead to disability and sometimes death. It is widely agreed that the optimal standard for haemophilia treatment is prophylactic substitution therapy, i.e. the regular infusion of the missing coagulation factor.

At the moment, a number of novel therapies, both substitutional and non-substitutional, are either being marketed in Europe or are in various stages of clinical development. As these therapies use medical technologies that have never before been used on patients for the duration of their lifetime, many questions arise with regard to their long-term safety and efficacy. In fact, currently only pre-clinical data for these therapies are available. However, we know that unexpected adverse events may take a prolonged time of use to become apparent and identified, in particular in a patient population affected by a rare disorder where no large cohorts of users can be set up. For instance, it took 25 years of use of current replacement therapy to identify that there are differences between plasma-derived and recombinant coagulation factor proteins with regard to inhibitor development in previously untreated patients (PUPs)[1]. Furthermore, pre-clinical studies are designed to demonstrate a desired effect in ideal conditions where patients are carefully selected to fit certain criteria and follow strict treatment protocols. Therefore, these studies are not ideal for identifying adverse events and demonstrating long-term efficacy.

These considerations led to discussions on whether current methods for collecting data on safety and efficacy are adequate for novel medical technologies in haemophilia and if not, what changes could be made.

Findings and discussions

Three types of novel treatments[2] in haemophilia with two main modes of action were discussed: the first, which extends the coagulation factor half-life using a tag added to the missing coagulation protein

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[1] Peyvandi F. et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. *N Eng J Med* 2016 (374):2054-2064.
[2] A thorough overview of new technologies for the treatment of haemophilia can be found in the EHC August 2016 Newsletter.

(substitution therapies), the second, which downregulates natural occurring anticoagulants in the patient's body and the third, which through the use of a bispecific antibody acts as a new by-passing agent and activates FX in patients with haemophilia A with and without inhibitor (non-substitution therapies).

For the first category of products, namely extended half-life products, the most pressing question is whether the exposure of the patient to a novel molecule, i.e., the tag used to prolong the protein's half-life, can cause long term side effects. Currently, three different tags are used to extend the half-life: polyethanol glycol (PEG), Immunoglobulin G fragment crystallisable region (Fc) and albumin. Potential undesired effects that could be seen with these products include toxicity, immunogenicity to either the tag or the product itself, allergic reactions and any unpredictable side effect. In particular, for products using PEG, there is a concern that the PEG, which is not completely eliminated by the body, may accumulate over time in the brain, liver or kidneys. This concern is aggravated by the intravenous injections for the duration of a lifetime. There are safety data from PEG products found in cosmetics and other medicinal products, but these are neither used intravenously nor for such a long duration. Available pre-clinical data are not sufficient to determine the long-term effects on the health of the patient.

Another concern related to these new technologies (both substitution and non-substitution therapies) is the lack of standardised laboratory assays to measure levels of coagulation factors. This could be critical in case of emergency medical procedures or if different types of products are used on the same patient (e.g., regular coagulation factors and extended half-life coagulation factors).

Furthermore, from preliminary clinical data it appears that some of the non-substitution therapies may lead to increased thrombogenicity, in particular when associated with replacement therapy used to treat acute bleeding or for surgery, or when combined with bypassing agents for the treatment of patients affected by inhibitors.

With regard to efficacy, current outcome measures used to determine products' efficacy include annual bleed rates (ABR), joint bleeds, the haemophilia activity list, quality of life and pain. With regard to ABR, the challenges with this parameter lie in the documentation (patient reported vs clinician reported bleeds), validation (limitation of imaging techniques and clinically silent bleeds) and categorisation (spontaneous vs traumatic bleeds and bleed severity). With regard to joint bleeds, they are considered to be the first cause of joint damage and as such, the health of joints is deemed to reflect the cumulative memory of the quality of the treatment. It is essential to avoid arthropathy because once it sets on, it cannot be stopped or reversed. Measuring arthropathy is, therefore, a very good indicator of the efficacy of a treatment, but it is difficult to measure due to lack of standardised methods to monitor its progress.

Another issue that should be taken into account when talking about efficacy is adherence to and individualisation of treatment. Without adherence, the patient will not achieve good outcomes. It is therefore critical to tailor treatment to each patient. This is particularly true for novel therapies, whose different mechanisms of action and extended half-lives may be adapted to offer either longer protection or higher coagulation factor trough levels depending on patients' needs.

The optimal method for measuring and monitoring both the efficacy and safety of a medicinal product is a randomised clinical trial (RCT). Although RCTs are also the ideal standard to measure unexpected adverse events, they are rarely feasible, particularly for rare disorders, or rare outcomes. Observational studies are deemed adequate to study adverse events, when these are unexpected, whereas for adverse effects that are known, they are likely to suffer from incomparability of groups (confounding by indication). When observational studies suffer from uncontrollable confounding by indication, as has been the case for the study of the effect of the type of haemophilia treatment on inhibitor development in PUPs, we should resort to RCT. This is why the results of the Survey of Inhibitors in Plasma-Products Exposed Toddlers (SIPPET – see footnote 1) are so significant. This study showed that the class of recombinant FVIII product carries more risk of inducing inhibitors in PUPs than plasma-derived FVIII. However, the debate amongst clinicians on how to implement the findings continues.

Another data gathering question that was discussed during the event was whether PUPs are the ideal patient population in which to study inhibitor development and other side effects. The premise for this question is that PUPs, with less than 50 exposure days, are more likely to develop inhibitors independently of the product used than previously treated patients (PTPs). The risk of developing inhibitors in PUPs is much higher than in PTPs, i.e. around 30 per cent vs less than 1 per cent per year. This means that if there is a spike in inhibitor development in PTPs, there is a clear signal that the product used in these patients is more immunogenic than other products on the market.

Currently, the European Medicines Agency (EMA) requires that studies on novel treatment for haemophilia be carried out in at least 50 PUPs in the pre-approval phase and in another 50 PUPs in the post-approval phase. This means that each new product needs to be tested on at least 100 PUPs - a high number for a rare disease population. Failing to carry out research in these PUPs will delay marketing authorisation and access to novel treatments. Additionally, it was noted that the number of PUPs needed in clinical studies for haemophilia treatment increased from 20 in 1995 to 100 in 2009, when the latest EMA guideline[3] on the subject was revised. Besides being a high number to recruit, 100 PUPs are also largely insufficient to provide meaningful information on the immunogenicity of new FVIII products. An alternative method to study the immunogenicity of novel treatments would be to monitor changes in immune biomarkers in patients exposed to new treatments. This would help to better understand the plasmatic and cellular immunology of inhibitor development.

Conclusions

There was general agreement amongst speakers and participants that there should be a coordinated effort between industry, patients and healthcare professionals to ensure that long-term post-marketing data are collected to monitor safety and efficacy. Participants agreed that with the advent of novel medicinal products, it is time to start collecting data, although some suggested that we may already be too late.

Participants highlighted the need to harmonise and standardise data collection to power post-marketing studies on the long-term effects of these treatments. It was noted that the Scientific and Standardisation Committee (SSC) of the International Society for Thrombosis and Haemostasis (ISTH) is developing a guideline with recommended minimal datasets for new haemophilia treatment products to monitor their safety. This guideline will be presented during the 2017 SSC-ISTH meeting. This will follow the 2015 SSC proposal on statistical methods and sample sizes for the design of clinical trials for new products in haemophilia[4].

It is recommended that post-marketing data should not only be collected in a standardised manner but also widely shared amongst all haemophilia centres to foster research.

Additionally, participants noted the need to standardise laboratory assays to monitor novel treatment levels in patients.

It is also suggested that since current pre-clinical studies do not have much power to identify adverse events, there should be a shift in clinical data used for marketing authorisation, in which fewer data on immunogenicity are required to license a novel therapy – particularly as immunogenicity is less relevant for non-substitution therapies. This must be coupled with a commitment by both regulators and industry to collect long-term structured post-marketing surveillance data.

Finally, it was noted that gene therapy is another novel treatment in haemophilia that is being developed. Participants wondered whether regulators had any strategy on how to include PUPs in gene therapy studies. As it was pointed out, currently no gene therapy study is enrolling PUPs, although this is the population that would benefit the most from such treatment. As there are clear ethical issues to be

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[3] Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009_rev. 1).

[4] DiMichele DM et al, J Thromb Haemost 2015; 13: 876-9.

considered, some participants voiced concerns over the fact that if clinical trials in novel therapies are conducted in areas with no access to treatment, there may be a risk of patients choosing to participate out of fear that trial enrolment is their only hope for treatment. The important role of an ethics committee in authorising clinical trials was highlighted.