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Event report: EHC Round Table on the Usage and Measurement of Extended Half-Life Coagulation Factors and Non-Substitutional Therapies

On Tuesday 28 November 2017, the European Haemophilia Consortium (EHC) held its third Round Table of Stakeholders of the year at the Sofitel Hotel in Brussels, Belgium. The event brought together over 40 participants representing researchers, industry, patients and the academia to discuss the usage and measurement of extended half-life coagulation factors and non-substitutional therapies.

The event's agenda, list of speakers and presentations can be consulted here or online on the EHC website. Pictures from the event can be viewed on the EHC Facebook page.

On the Usage and Measurement of Extended Half-Life Coagulation Factors and Non-Substitutional Therapies

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.

Extended half-life (EHL) coagulation factors are clotting factors which stay in the patient's blood circulation longer than the usual clotting factors. This means that a patient could infuse less often than usual, which would give him a much-needed flexibility.

Findings and discussions

Bleeding episodes are a reality for people with haemophilia and it is essential to prevent them as much as possible. As mentioned above, the optimal standard for haemophilia treatment is prophylactic substitution therapy. However, frequent intravenous infusions are a burden, while patients still experience bleedings despite prophylaxis. What is more, there is a 33 per cent risk of developing inhibitors and the treatment for these patients becomes less effective. It is for these reasons that the need for other, improved products is evident. While according to studies many patients are ready to switch to EHL products, others have their doubts due to uncertainties about safety in new products, inhibitor risk, immediate availability of current product, etc. As for the modalities of making the choice to switch to an EHL product, it was noted that from a patient perspective the most important factors are bleeding rates, venous access and convenience, while for the prescribing treatment centres, it is the cost.

Monitoring, efficacy and safety for EHL and non-substitutional therapies

It became apparent from the discussions that in terms of monitoring efficacy in the lab:

- EHL rFVIII (so far) can be monitored with chromogenic assay (CSA)
- EHL rFIX requires different monitoring depending on the product
- Non-substitutional products are unlikely to use routine assays
- Better communication will be required between treatment centres and laboratories
- It is now vital that clinicians and laboratories understand their reagents' profiles

In terms of monitoring safety for EHL and non-substitutional therapies, it is imperative from the regulator's perspective to ask companies for as much data on safety as possible. During the Round Table, the case study of Refixia was presented. Refixia is a purified recombinant human factor IX (rFIX) with a 40 kDa polyethylene-glycol (PEG) selectively attached to specific N-linked glycans in the rFIX activation peptide. During trials, it was observed that PEG may build up and cause side effects. Therefore, the European Medicines Agency (EMA) decided for risk minimisation measures, including labelling the medicine with a black triangle, indicating that it is being monitored particularly closely by regulatory authorities, and asking physicians to report suspected adverse reactions. The have also set an age restriction, licensing only for above 12 years old.

Regarding the safety perspective for gene therapies, the EMA noted that a thorough understanding of the mechanism of action of the vector and its gene product, and their associated risks, needs to be determined in non-clinical and clinical studies prior to submission of a marketing authorisation application (MAA). In addition, there is a need for a long-term follow-up of the patient post-administration in order to fully understand the long-term safety and efficacy. Finally, the EMA is engaging with the FDA on upcoming novel haemophilia therapies.

Assessing value: standard treatment vs novel technologies

When assessing the value of standard treatment against novel technologies, it is crucial to define what value are we looking for. During the EHC Round Table the following concepts were discussed – safety, effectiveness, availability, ease of use, lifecycle costs and financial acceptability. Speakers stated that national procurement of factor concentrates can help to ensure that people with haemophilia, von Willebrand disease, and other inherited bleeding disorders have access to treatment that is not only sufficient in quantity, but also meets the required standards in relation to safety, efficacy, and quality. It was noted that health technology assessment (HTA) agencies look at the incremental cost per quality-adjusted life year of any change in product or the additional benefit that a new generation of product would possibly provide. The agencies may not approve reimbursement of new products, especially if the incremental cost or the total budget increases significantly.

It was noted that national procurement has secured economically advantageous contracts for clotting factor concentrates (CFCs) in many countries to date, but there is still a need for optimized selection criteria for novel technologies. In addition, there are still challenges in terms of validation of novel therapies in the real-world. Ongoing collaboration between patient organisations, treaters, payers, health economists and the pharmaceutical industry is vital to achieve value when assessing novel technologies.

What will haemophilia look like in 2027?

Current ambitions in haemophilia therapy are: zero bleeds, zero infections, zero inhibitors (all achievable except the last one).

What will happen during the next 10 years: Will the minority of already well treated patients have access to more convenient and efficient therapies? Will the vast majority of patients who have no or limited access to treatment and care be treated with replacement therapy? Will all patients have access to more convenient and efficient therapies? Those were some of the many questions which participants tried to answer during the Round Table discussion.

There are some great strengths in the FVIII replacement therapies, such as the fact that they can be given to all haemophilia patients without inhibitors, have rapid onset action and are easily assayed amongst others. However, these therapies require multiple infusions, are burdensome and are not always fully effective. One thing is certain – novel therapies are coming down the line, but the future will depend on the further validation and safe introduction of these therapies. In this sense, the UK National Institute for Health and Care Excellence (NICE) is also looking into how to create a level playing field between different diseases to make the correct decisions.

Predicting the future is always a risky business. However, it can be anticipated that standard and longer-acting CFCs will still be used routinely. Perhaps more than one non-substitutional therapy will be widely used, including drugs targeting physiological anticoagulants. In 10 years' time, the haemophilia care will have been transformed in an unprecedented way. Many questions will have to be answered and we have to advocate the pursuit of these answers, while as a community, people with haemophilia have to get comfortable with the new language of novel therapies and prepare to take firm positions.

Conclusions

It is not excluded that novel therapies could become available for patients not only in developed but also in emerging countries. However, and as rightfully pointed out during the presentations, it is always tricky to predict the future. The only certain thing is that it would be different, as every product, including FVIII replacement therapies, has its strengths and weaknesses. While they are efficient for treatment of bleeds and in surgeries and they have the trust of patients and doctors, they are still burdensome and not fully effective. If patients and clinicians get more data and a deeper understanding of the benefits and possible risks of EHL and novel products after it, it will be a new landscape for haemophilia. This is exciting, but with opportunity comes great responsibility and all stakeholders - patients, clinicians,

laboratories, regulators and payers - will need a "re-education" to navigate the brave new treatment world upon us.