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Event Report: EHC Round Table of Stakeholders on 'Inhibitors in Haemophilia A'

About the event

On Tuesday 16 February 2016, the European Haemophilia Consortium (EHC) held a Round Table of Stakeholders at the Royal Windsor hotel in Brussels, Belgium, to discuss the topic of inhibitors in haemophilia A. The event gathered over 75 participants including patient representatives, healthcare professionals, representatives from the pharmaceutical industry and regulators. A full list of speakers can be found here. The full agenda of the event can be found here. Presentations from the event can be found here.

About inhibitors

Haemophilia A is a rare and congenital bleeding disorder caused by a genetic defect resulting in a lack of or insufficient coagulation factor VIII in the body. This causes, in affected individuals, an inability to clot blood, leading to bleeds in the joints, muscles and soft tissues. If left untreated, this can cause disability and sometimes death. About 30 per cent of patients with haemophilia A will develop inhibitors to their treatment within the first 50 exposure days (EDs). When affected by an inhibitor, patients are no longer able to rely on traditional replacement treatment and are left more vulnerable to bleeds. Eradication of inhibitors, i.e. Immune Tolerance Induction (ITI), is effective in approximately 70 per cent of patients, however inhibitors can re-appear after treatment. Additionally, it is a costly treatment, which means that resource-limited countries are often unable to offer this therapy to people with haemophilia and inhibitors (PWI).

Inhibitor development is therefore seen as one of the greatest medical challenges in haemophilia treatment, and although scientists have identified some genetic factors that may increase its incidence, the exact development mechanisms remain unclear. One hypothesis has been that some types of coagulation factors (namely recombinant products) could increase the chances of inhibitor development compared to other types of coagulation factors (namely plasma-derived treatment). These assumptions have been based on a series of observational studies. To confirm this hypothesis, a team of scientists conducted a randomised clinical trial (RCT): the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET)[1], using both available types of replacement therapies (i.e. plasmatic and recombinant coagulation factor concentrates) at random in over 200 patients. The results of the study point to patients who received recombinant products developing more inhibitors than patients who received plasma-derived products. Despite these study results, many controversies remain.

In light of these scientific findings, and coinciding with the launch of a new programme to better support patients with inhibitors, the EHC organised a Round Table of Stakeholders on Inhibitors in Haemophilia A to bring together several experts and discuss this topic.

Findings and discussions

EHC European Inhibitor Network

PWIs are more prone to disability, social isolation and financial difficulties compared to people with haemophilia without inhibitors. As inhibitors affect a minority of their members, national patients'

[1] At the time of the event, the final results of the SIPPET study had not yet been published. The full study was subsequently published in the *New England Journal of Medicine*.

organisations cannot offer adequate support services to this subgroup of patients. This is why the EHC developed a new European programme: the European Inhibitor Network (EIN) to support PWIs. The components of this programme were presented during the event.

Challenges in inhibitor treatment

At the moment there is no agreed protocol on treating PWI; instead, various strategies exist. This is largely due to uneven product availability in each country. PWI are generally managed with bypassing agents, i.e. molecules that trigger the coagulation cascade and clotting without generating an immune response. However, the half-life of these products is short and there are no clear assays to measure factor activity. Nonetheless all available bypassing agents are effective at preventing and treating bleeds. Unfortunately, their short half-life means daily infusions for prophylactic treatment, which could damage venous access. An alternative to the administration method is the use of a central venous access device, which needs to be surgically implanted and removed every few years and which can lead to infections.

ITI, i.e. the continuous infusion of high-dose coagulation factors, is seen as a cost-effective treatment for eradicating inhibitors, in particular in children. If successful, ITI can improve joint preservation and increase quality of life. However, it is very costly and not available in all countries; also only 70 per cent of ITI is successful.

It was also noted that inhibitor development is increasingly detected thanks to improved diagnostics. This fact should be taken into account by governments and regulators to better plan resources for haemophilia care. Additionally, it was stressed that the use of registries and national tenders can make the organisation of haemophilia care more cost-effective.

Finally novel therapies, such as for example extended half-life treatments, could offer an alternative for people with inhibitors, however measures need to be implemented to monitor and collect data for long-term safety.

Data collection and post-marketing surveillance

As to data collection on inhibitor development there are different approaches (e.g. clinical studies for product licensing, patient registries and national databases leading to observational studies) whose results are difficult to aggregate. At the moment recommendations on data collection are being developed by the International Society for Thrombosis and Haemostasis (ISTH). However, collection of quality data is resource-intensive not only for healthcare professionals collecting the data but also for patients reporting the data.

SIPPET study and its implications

The findings of the SIPPET study, the first RCT looking at inhibitor development in haemophilia, noted that inhibitor incidence in previously untreated patients (PUPs) was 27 per cent when using plasma-derived coagulation factor concentrates and 44 per cent when using recombinant products. These much-awaited results were closely scrutinised by regulatory agencies in Europe, who are now considering whether to change guidelines for the treatment of PUPs with haemophilia. However, this study does not seem to close the debate on inhibitors as some question the conclusiveness of the study.

Conclusions

Participants agreed that the choice of treatment product should be made jointly by the patient and the physician. Furthermore, countries that cannot provide ITI or bypassing agents to their PWI should consider treating PUPs with plasma-derived treatments and then switching them (if they wish to) to recombinant products after 50 EDs. This should also be considered for patients that are at greater risk of developing inhibitors (due to family history and genetics). Experiences from countries with national tenders have shown that switching type of treatment does not cause a significant increase in inhibitor development. With regard to safety, it was noted that no viral transmission had occurred with plasma-derived products in almost 30 years, thanks to stricter safety measures both in blood collection and the manufacturing process. Nonetheless, there is always a potential risk of contamination with emerging and unknown pathogens. Participants concluded that ultimately patients should be informed about treatment products and allowed to make their own choices about their treatment.