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EHC Round Table of Stakeholders

Factor Concentrate-Related Inhibitor Risk in Haemophilia A

Meeting Report

Royal Windsor Hotel, Brussels, 2 March 2015

Executive Summary

On 2 March 2015, the European Haemophilia Consortium (EHC) hosted its first Round Table of the year at the Royal Windsor Hotel in Brussels. The event aimed to present an overview of the current findings on the risks associated with inhibitor development when using different types of factor concentrates in previously untreated patients (PUPs). The event featured several presentations summing up findings from studies such as the Research Of Determinants of INhibitor Development among PUPs with haemophilia (RODIN), UKHCDO, FranceCoag and the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET).

Prof Michael Makris, member of the EHC Medical Advisory Group and chair of the event, stated in his opening address that inhibitors are the major challenge in haemophilia care today. In fact, the mechanisms and factors contributing to inhibitor formation are still poorly understood by the medical and scientific community. The development of inhibitors has devastating consequences for patients both physically and emotionally as it leaves people affected by inhibitors at greater risk of disability and death. Furthermore, inhibitors are extremely expensive to treat, which results in even poorer access to treatment in resource-limited countries.

Presentations and discussions during the Round Table showed that inhibitor development is a multi-factorial event in which both genetic and external factors, such as treatment regimens, contribute to inhibitor formation. Professor Pier-Mannuccio Mannucci (University of Milan) discussed the controversial issue of whether recombinant concentrates cause more inhibitors in PUPs than plasma-derived products. He ended by presenting the SIPPET trial, which is examining this issue in a randomised manner and the results of which are awaited with great interest.

Other speakers focused on the issue of whether different recombinant concentrates are associated with different inhibitor risks. Professor Jenny Goudemand (University of Lille) presented the data of the RODIN, UKHCDO and FranceCoag studies, which suggested that second generation concentrates had a higher inhibitor risk in PUPs as compared to third generation concentrates. Dr Kathelijn Fischer (University of Utrecht) showed the EUHASS data, which did not find a difference between different brands of concentrates. Dr Alfonso Iorio (McMaster University) discussed all the studies to date and suggested that the issue may not be as clear-cut as has been suggested because the risk in inhibitor development for both recombinant and plasma-derived coagulation factors varies greatly depending on the study and centre administering the product. Prof Frits Rosendaal (University of Leiden), invoked the *in dubio abstine* principle of modern medicine and recommended avoiding the use of any product against which concern has been raised, if an alternative is available. Other speakers, however, claimed that the only way to be sure about whether or not a particular product has an increased effect on inhibitor formation is to run a randomised controlled trial.

Speakers included:

- Prof Michael Makris, EHC Medical Advisory Group and University of Sheffield
- Prof Pier-Mannuccio Mannucci, University of Milan
- Prof Jenny Goudemand, University of Lille
- Dr Kathelijn Fischer, University of Utrecht
- Dr Alfonso Iorio, McMaster University
- Prof Frits Rosendaal, Leiden University
- Mr Thomas Sannié, French National Member Organisation (NMO)

On 2 March 2015, the European Haemophilia Consortium (EHC) organised its first Round Table of the year on: 'Factor concentrate-related inhibitor risk in haemophilia A.' The event was chaired by Prof Michael Makris (University of Sheffield), member of the EHC Medical Advisory Group, who opened the Round Table by stating that inhibitor development, and not the cost of treatment, is the real challenge in haemophilia care today.

Plasma-derived factor VIII versus recombinant factor VIII

Prof Makris gave the floor to the first speaker, Prof Pier-Mannuccio Mannucci, from the University of Milan. Prof Mannucci spoke about the development of inhibitors and gave an update on the Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) trial. Prof Mannucci started his talk by explaining that the development of inhibitors involves many factors including treatment, but also, and perhaps most importantly, patient's genetics, the severity of haemophilia, the FVIII mutation and the family history, as well as environmental factors such as immunisation, bleeding events and surgery.

With regard to products, he compared plasma-derived factor VIII (pdFVIII) with recombinant factor VIII (rFVIII) and noted that these products were different in their origin and production and also in their content of von Willebrand Factor (VWF), which is higher in pdFVIII. Furthermore, pdFVIII also contains other human proteins, which may play a role in inhibitor formation.

Current studies carried out on this issue do not provide any conclusive results because they were heterogeneous in their design and their choice of patient population. Furthermore, results within each cohort (pdFVIII versus rFVIII) showed some significant discrepancies. For instance, on average the incidence of inhibitor development in PUPs using pdFVIII is 14 per cent, however amongst the studies using pdFVIII some show an incidence of inhibitor development as high as 30 per cent. On the other hand, studies using rFVIII in previously untreated patients (PUPs) have an average incidence of inhibitor development of 31 per cent. Nonetheless, some studies using rFVIII show an incidence in inhibitor development lower than 10 per cent. This demonstrates that it is not possible to rely on existing studies to determine whether the use of pdFVIII or rFVIII are associated with a real difference in inhibitor development.

The Research Of Determinants of INhibitor Development among PUPs with haemophilia (RODIN) study is the largest multicentre observational cohort study in terms of number of patients (574 severe haemophilia A PUPs) and exposure days (29,679 days). The results of this study showed similar incidence rates for pdFVIII and rFVIII at around 32 per cent. However, Prof Mannucci pointed out that the study had limitations, primarily in the lack of randomised assignment of product. Furthermore many patients on pdFVIII were treated with monoclonal FVIII and the results were aggregated with those of VWF-rich products. Finally, pdFVIII treated patients only made up a small percentage of the study (4,018 exposure days for pdFVIII versus 26,661 for rFVIII).

It is for the reasons mentioned above that Prof Mannucci and other physicians decided to launch a randomised (but not blind) controlled trial five years ago: the SIPPET trial. The trial assumes that all FVIII products are equally efficacious and broadly equivalent pertaining to their capacity to control a bleed. Hence, the study is based on the randomised comparison of two classes of FVIII products (pdFVIII with VWF and rFVIII with no VWF) to see what their impacts are on inhibitor development. The trial has been funded by the Italian Ministry of Health and by several pharmaceutical companies. So far, 300 patients have been recruited, 260 have been enrolled and 240 are being treated. Patients selected had no inhibitors at baseline and the main endpoint was all neutralising antibodies, while the secondary endpoint was high baseline inhibitors. The study is conducted worldwide and includes 61 centres with 60 per cent of patients being treated in Africa and Asia.

Currently, 70 per cent of patients enrolled have completed their first 50 exposures within three years. At the time of the interim trial analysis, the incidence of inhibitors was 29 per cent. Half of the patients had low titre inhibitors and half had high titre inhibitors.

Prof Mannucci proceeded to provide additional information on the data analysis. He explained that the interim report was done by Prof Frits Rosendaal from the University of Leiden in the Netherlands, who was also a speaker at the Round Table. The outcome of the interim analysis was that the study is safe to continue; that there is no futility[1] issue to stop the study from continuing and that going forward it is critical to maintain the data in confidence in order to preserve the integrity of the study. Finally, it was determined that the original hypothesis of SIPPET of an at least two-fold lower incidence of inhibitors with pdFVIII and VWF-containing products is still viable and valid.

In conclusion, Prof Mannucci stated that both sources of FVIII (pdFVIII and rFVIII) are needed at present and in the future. Although higher pathogen safety is perceived as an advantage in recombinant products, lower immunogenicity is perceived to be the main advantage of plasma-derived products.

Nonetheless, there is not enough pdFVIII to meet the current and future needs of patients and longer-acting products are all based on recombinant DNA technology. In the end, he underscored that the choice between the two products has to be made by fully informed patients and that choice should be respected.

Following the presentation, there were questions from the audience and Prof Mannucci explained that the testing on inhibitors was centralised. The first notice of inhibitors is given by the local centre (i.e. the centre closer to the patient) but the confirmation was done by the centralised centre in Milan, Italy.

Other questions included whether Kogenate had been used in SIPPET and if it had an impact on inhibitor development. Prof Mannucci reported that Kogenate was indeed used and that at the moment he was unable to give any results.

Second generation versus third generation factor VIII products

The second presentation was given by Prof Jenny Goudemand from the University of Lille in France. Prof Goudemand addressed the issue of the inhibitor risk with second versus third generation FVIII products.

She started her presentation by stating that for several years pdFVIII and rFVIII were compared as two homogenous groups, and patients were regrouped according to the type of products they were treated with. However, the RODIN study found an unexpected result, which was that there were fewer differences in the two categories (plasma-derived versus recombinant) than between different generations of the same category of products. In particular, the second generation full length FVIII showed a significant increase in the risk of inhibitor formation in PUPs.

Prof Goudemand explained that over time manufacturing techniques (animal and human protein removal techniques) for FVIII and the understanding of co-factors influencing inhibitor development (such as genetics and environmental factors) have improved. This is why with historic studies these co-factors associated with inhibitor development were not reported, and the studies focused primarily on the product. She noted that it is important to keep in mind that products were not marketed and studied at the same time and older studies lacked current knowledge. For instance, when studies with Advate were carried out, the knowledge of co-factor risk was improved and it was possible to collect information about other risks such as the intensity of treatment and the exposure to surgery. This is referred to as the *calendar effect*.

Following this introduction, Prof Goudemand proceeded to compare four studies that used various FVIII products, including third generation rFVIII Advate (Baxter) and second generation rFVIII Kogenate (Bayer). These included the RODIN study, the study from the Réseau FranceCoag[2], a study from the UK Haemophilia Centre Doctors' Organisation[3] (UKHCDO) and a Canadian cohort study[4]. When the inhibitor

[1] The term 'futility' is used to refer to the inability of a clinical trial to achieve its objectives.

[2] Calvez, Chambost, Claeyssens-Donadel, et al. Recombinant factor VIII products and inhibitor development in previously untreated boys with severe haemophilia A. *Blood* 2014; 124(23):3398-3408.

[3] Collins, Palmer, Chalmers, et al. Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe haemophilia A, 2000-2011. *Blood* 2014; 124(23):3389-3397.

risk was adjusted to all the other genetic and non-genetic risk factors, the studies showed that Kogenate had a higher inhibitor risk. Prof Goudemand proceeded to review potential reasons for this finding. For instance, both the UK and the French studies were divided in three and four time periods, respectively, to see if the *calendar effect* explained above could be the source of the problem. The French study showed that there was a slight increase in inhibitor risk over time, while the UK study concluded that the most peak time for inhibitor development was between 2005 and 2008, which contradicted the findings from the French study.

In conclusion, the data collected needs to be checked to exclude any bias and researchers need to remain conscious of the interpretation of the final data. This data will be submitted to the European Medicines Agency and a suggestion will be made for pooled analysis of individual available data.

Finally, Prof Goudemand explained that the first step was the comparison of patients treated with different generations of rFVIII and that the next step will be to compare rFVIII with pdFVIII. The current issue in studying this difference is that pdFVIII is perceived to be less immunogenic than rFVIII, so the risk is that patients with increased co-factors for inhibitor development (such as genetic and environmental co-factors) may have been treated with pdFVIII and scientists will need to be aware and conscious of this difference. Also, for some patients there may be a bias to use pdFVIII and for some countries it is the product of choice. All of these aspects will need to be taken into account.

Report from the European Haemophilia Safety Surveillance (EUHASS)

The next presentation was given by Dr Kathelijn Fischer from the University of Utrecht in the Netherlands. She gave a report on the data collection of the European Haemophilia Safety Surveillance (EUHASS), a prospective European surveillance system that started in October 2008. Data is submitted four times a year by 74 centres and only data that is verified is analysed. There is no central testing and all analysis is performed by local centres. With regard to inhibitors in PUPs, data is submitted on PUPs reaching 50 exposures without inhibitors.

So far, it was noted that the incidence rate for inhibitors is 26 per cent. The study shows that there is no significant difference in inhibitor development between pdFVIII versus rFVIII and also in second versus third generation FVIII products. However, data from other studies such as RODIN, Réseau FranceCoag and UKHCDO suggest otherwise. The baseline risk for Helixate/Kogenate ranges from 25.9 per cent in EUHASS to 37.6 per cent in the Réseau FranceCoag study. Dr Fischer showed that only limited numbers of patients and centres overlap between RODIN, Réseau FranceCoag, UKHCDO and EUHASS.

Dr Fischer proceeded to question why there were such high differences. She noted that the patient characteristics are similar as all studies report on the treatment of PUPs. Therefore she assumed that the changes may lay in either the data collection and analysis or the treatment regimens and product selection by the treatment centre. With regard to data collection and analysis, Dr Fischer stated that the EUHASS method is different, and assumes that the rate of the use of concentrates was constant. This could be biased by the introduction of new concentrates. Furthermore, the cohort studies follow patients for 50 exposure days from first treatment, while the EUHASS study is calculated from the moment that the patient develops an inhibitor or when they reach 50 exposure days without an inhibitor. With regard to concentrate selection, the main difference was noted in RODIN versus non-RODIN centres. In fact, almost half of the RODIN centres (49.7 per cent) used Advate while Kogenate was more widely used in non-RODIN centres (43 per cent), although this is believed not to be significant. With regard to data of previously treated patients (PTPs) there is a small non significant difference when using Kogenate (1.3/1000 pt yrs[5]) compared to Advate (1.1/1000 pt yrs).

In conclusion, the difference in data collection can explain some differences between the incidence in inhibitor risk for Kogenate between EUHASS and other studies, but it cannot explain everything. Dr

[4] Vézina, Carcao, Infante-Rivard et al. Incidence and risk factors for inhibitor development in previously untreated severe haemophilia A patients born between 2005 and 2010. *Haemophilia* 2014; 20:771-776.

[5] Pt yrs = patient years; a statistic used to represent incidence rate

Fischer hypothesised that this could be explained by treatment selection. The next step will be pooled analysis of the RODIN, Réseau FranceCoag and UKHCDO studies.

Finally, Dr Fischer explained that a clear way to determine whether Kogenate increases the risk of inhibitor formation compared to other products, such as Advate, would be to run a randomised controlled trial (RCT). However, to accomplish this, the number of patients would have to be considerable and the ethics would be questionable.

Following her presentation, the floor was opened for questions. One of the participants noted that in one of Dr Fischer's slides there seemed to be different trends in the development of inhibitors in haemophilia A and B. Dr Fischer stated that this was due to the low numbers collected for haemophilia B, which cannot be used reliably as they have little statistical significance.

Other participants noted that randomised studies are usually not carried out to determine side-effects and as inhibitors are very frequent, these studies should not be carried out.

During the discussions it was also noted that it is a known fact that treaters have bias with regard to different products and treatment regimens. It is true that through a RCT, one could remove the treaters' bias.

Members of the audience noted that there were ethical concerns on running a RCT with products such as Kogenate and Helixate where there is evidence to suspect an increased risk in inhibitor development.

Finally, participants suggested that treaters could be surveyed to better understand the bias and selection process for products prescribed to patients. Dr Fischer confirmed that it was true that there were almost no centres prescribing only one factor concentrate, so it would be interesting to see on which basis different products are used on different patients. In addition, the cost of the product should also be taken into consideration as prices may fluctuate from one year to another.

Critical Appraisal of the data on inhibitor risk in PUPs

The next presentation was given by Dr Alfonso Iorio from McMaster University in Toronto, Canada. His presentation focused on introducing methodology to assess causality and to appraise the data on the concentrate-dependent risk of inhibitors.

Dr Iorio started his talk by explaining that it was important to be able to properly assess a causation link between two phenomena; in this case exposure to a particular factor concentrate and the development of inhibitors. Dr Iorio gave as an example the causation of cancer by smoking cigarettes and cigars. He stated that there is now strong evidence of causation between these two phenomena. Nonetheless, he also noted that statistically people who carry matches or lighters are also more at risk of developing cancer. In this case the action of carrying such items does not in fact cause cancer but rather reflects the fact that these items were generally carried for the purpose of smoking. With this example in mind, he noted that when trying to assess causation it is important to perform a multi-variate analysis, which also looks at the interaction of different factors to see if more than one variable might be having an effect on the outcome (e.g., in the case of inhibitor formation, the brand, family history, gene mutation).

Dr Iorio also noted that there may be some unknown factors influencing causation and that these unknowns make it difficult to calculate the probability of causation, since that they cannot be taken into account. This is the case also for inhibitor formation. As the other speakers noted, in earlier studies many genetic and environmental factors related to the patient were not taken into account, even though they have an impact on inhibitor formation.

For this reason, Dr Iorio stressed that RCTs were far more reliable than observational studies and he proceeded to provide several examples in other medical areas where the observational study showed one thing and the results from the RCT showed the opposite outcome. Furthermore, there may be other factors such as the doctors' bias towards certain products.

He then proceeded to review the results of various studies including RODIN, Réseau FranceCoag, the UKHCDO, the Canadian cohort, EUHASS and data from a European Association for Haemophilia and Allied Disorders (EAHAD) project. Dr Iorio pointed out that in his opinion the RODIN study lacked transparency in its reporting, that there was no mention of the interactions and that the variation between centres was not explored. He also noted that in the FranceCoag study, the high level of inhibitors came primarily from three centres. All other centres in the Francecoag study show equal development of inhibitors. This led to the question about whether the increase in inhibitor formation was caused by other factors such as treatment regimens and product selection. With regard to the incidence of inhibitor development when using Kogenate, it varies between 16 to 50 per cent across the different studies. This is very hard to explain because if the product were the main cause of the inhibitor risk the incidence would be more consistent. Furthermore, Dr Iorio noted that in all studies there was a *calendar effect*. Dr Iorio commented on the work done by EUHASS on the collection of data, which is comparable to the RODIN study but was done more quickly. He stated that the EUHASS data is, as previously demonstrated, discordant with the previous studies.

In conclusion, Dr Iorio noted that additional studies were needed to properly assess whether Kogenate is more immunogenic as current results are unclear. Finally, he stated that in his opinion the only way to be certain about this product would be to run a RCT, though he admitted that ethical questions remain.

An epidemiologist's perspective

The next presentation was from Prof Frits Rosendaal from the University of Leiden in the Netherlands. Prof Rosendaal started his presentation by stating that side effects are often unexpected and unpredictable. They have different effects than the intended effect. They have a low incidence, and they are generally detected in the post-marketing phase. They are often not a class effect, because they are not based on the molecule with the intended effect. This is why causes for side effects are difficult to predict. Prof Rosendaal added that side effects generally pose major financial threats and that doctors feel uncomfortable about them because they prescribed the medicine that caused them.

Prof Rosendaal continued by explaining that RCTs are done to determine the effects of the treatment and they are not required to determine side effects. In fact, as side effects are not predictable, they are already randomised just by prescribing the medicine to different patients. Therefore, Prof Rosendaal stated that in his opinion randomisation for side-effects already took place in earlier studies on inhibitors and haemophilia.

Having said this and having reviewed the findings of the studies presented during the event (SIPPET, RODIN, Réseau FranceCoag and UKHCDO), Prof Rosendaal noted that in his opinion there is a reasonable doubt that links the use of Kogenate to an increased risk of inhibitor formation. He proceeded to ask, when there is a suspected adverse event, how much evidence is needed before it can be accepted that the product may have a higher risk of causing side-effects. He noted that the principle *in dubio abstine* should be used. This is a principle used in modern medicine, which suggests that when there is uncertainty, one should refrain from acting. Prof Rosendaal noted that alternative treatments exist on the market and that in his opinion the safety of patients should come first. For Prof Rosendaal, the RODIN study was the signal suggesting the potential causation between the use of Kogenate and the risk of inhibitor development and that other studies confirmed the signal. In his opinion, what remains to be done is to discontinue the use of Kogenate in PUPs and look at whether this could have been found out earlier.

Patients' role in reporting side effects

The final presentation was given by Mr Thomas Sannié, President of the French NMO. Mr Sannié stated that patients should report adverse events (AE) because there is underreporting from healthcare professionals. Furthermore, in his opinion, patients need to be aware that medicines have benefits but they also involve risks. Patients can support improving the knowledge about a medicine by providing

feedback on the benefits but also on the AE. Finally, reporting will increase the general safety level of a medicine and increase patient empowerment.

In 2014, the French Haemophilia Association decided to apply for funds from the French Medicine Agency (ANSM) for a project on patient reporting on side effects. The Association intended to raise awareness about side effects but also to encourage patients to report these events. The project resulted in a patient-friendly website providing a wealth of resources explaining how patients can report side effects, including videos, a poster and leaflets.

Mr Sannié concluded his presentation by showing an excerpt of a video explaining to patients why and how they can report side effects.

Discussions

Participants praised the French initiative stating that it was important to report not only inhibitors but also other side effects, which are often overlooked. Participants also suggested that this material should be translated into other languages.

During the discussions, it was noted that it had not been possible to foresee the potential side-effects of Kogenate at an earlier date. Participants discussed on whether additional data could be collected through a working group of the International Society of Thrombosis and Haemostasis.

A representative from Bayer noted that overall the studies mentioned during the event illustrated the high degree of variability for the risk of inhibitor development for the same product across different studies. The possibility of patient selection bias (i.e. the preferential use of Kogenate FS/Bayer in patients at higher risk for inhibitors) should be carefully considered, given the initial low inhibitor incidence of Kogenate in the earlier studies. Finally, the findings of the FranceCoag and UKHDCO PUPs papers are not well explained by altered immunogenicity of the molecule. Bayer investigated any molecular characteristics between Advate and Kogenate, and could only find minor, if at all any, differences between the two with regards to glycosylation and other protein characteristics.

Conclusion

In the light of all the presentations and discussions held during the meeting, there was a general consensus that additional evidence is needed to determine whether any single product increases the risks of inhibitor development. Although some speakers claimed that when in doubt physicians should abstain from prescribing a particular product, if alternatives are available, others insisted that the only way to be certain whether a particular product increases risks of inhibitor development is to run a RCT.

Finally, speakers agreed that earlier studies did not take into account other factors (such as genetic and environmental effects) that also impact inhibitor development. Current studies are trying to capture these factors, hoping that this will help researchers and physicians to gain a better understanding of the mechanisms responsible for inhibitor development.