

EHC Round Table of Stakeholders

Von Willebrand Disease and Factor: Current Clinical Issues

Meeting Report

Royal Windsor Hotel, Brussels, 16 June 2014



Executive Summary

On 16 June 2014, the European Haemophilia Consortium (EHC) organised its second Round Table of Stakeholders in Brussels, Belgium, to bring the EHC membership up to date on the current clinical developments in von Willebrand Disease (VWD) and factor (VWF). The event brought together around 40 participants representing the EHC membership, physicians, industry and other interest groups such as hospitals and hospital pharmacists.

Prof Paul Giangrande, chairman of the EHC Medical Advisory Group (MAG), chaired the event and opened the session by indicating that although VWD is one of the most common bleeding disorders, it is still largely under-diagnosed due to the fact that its symptoms are often treated individually and not seen as part of another condition.

The event then proceeded with two main topics: clinical developments in the diagnosis and treatment of VWD and the role of VWF in the prevention of inhibitor development. A final talk looked at the latest findings in the diagnosis and treatment of acquired von Willebrand syndrome (AVWS).

A few findings emerged from the presentations and discussions. It appears that VWD is still a difficult disease to diagnose, as demonstrated by Ms Baiba Ziemele, who currently still has no certainty about which type of VWD she is affected with. Diagnosis should be based on VWF levels but also on family history and the bleeding score. As a result of the difficulty in diagnosis, we note both over-diagnosis and under diagnosis of the disease currently taking place in developed and developing countries respectively.

VWD affects both primary and secondary haemostasis. This is caused by the dysfunction of platelet adhesion and the reduction of factor VIII activity in plasma. The therapeutic options should correct both defects. In terms of treatment regimen, this will vary greatly depending on the type of VWD affecting an individual but also depending on the bleeding profile. For patients with severe VWD and suffering from a greater number of bleeds, prophylaxis should be considered. However, it is important to note that this treatment course is quite expensive and may not be available in all European countries. Ultimately, the treatment regimen should be designed in accordance between patients and physicians. From the discussions it emerged that at the moment there are enough satisfactory treatments for this condition, however there are challenges in accessing these treatments, performing the right diagnosis and determining the correct treatment regimen for each patient.

With regard to the role of VWF in preventing inhibitor development, it appears that there is still great uncertainty regarding whether VWF does in fact play a role. Both presenters on this topic concluded that further research was needed.

Finally, AVWS is an acute syndrome, which takes place later in life and often following surgery or cancer treatment. It was noted that most patients affected by this syndrome go into complete remission, however timely diagnosis and treatment greatly improve morbidity rates.

The presentations were followed by lively discussions in which several people affected by VWD were able to share their experiences on living with the disease and accessing correct diagnosis and treatment.

Speakers at the Round Table included:

- Dr Antoine Rauch, University of Lille, France
- Ms Baiba Ziemele, President of the Latvian Haemophilia Society, Latvia
- Dr Susan Halimeh, Gerinnungszentrum Rhein-Ruhr, Germany,
- Prof Pier Mannuccio Mannucci, University of Milan, Italy
- Dr Carmen Escuriola-Ettingshausen, Haemophilia Centre Rhein Main, Germany
- Dr Srini Kaveri, Centre de Recherche des Cordeliers/ INSERM, France
- Dr Augusto Federici, University of Milan, Italy

Introduction

On 16 June 2014, the European Haemophilia Consortium (EHC) organised its second Round Table of the year on 'Von Willebrand Factor and Disease: current clinical issues.' The event, held in Brussels, examined the latest developments in the diagnosis and treatment of von Willebrand Disease (VWD) as well as the impact of von Willebrand factor (VWF) on the prevention of inhibitors in severe haemophilia. Prof Paul Giangrande, chair of the EHC Medical Advisory Group (MAG), chaired the event.

He opened the session by outlining the event's objectives and some of the current questions regarding the treatment of the condition. He explained that individuals with VWD symptoms such as menorrhagia (heavy periods) are rarely tested for bleeding disorders and routinely only more common causes (e.g. gynaecological) of abnormalities are taken into account, which makes the diagnosis particularly difficult and which leads to a low rate of diagnosis (as is the case with many other rare diseases). He also explained that patients' organisations have an important role to play in raising awareness.

Raising awareness about VWD

The first presentation from Dr Antoine Rauch, a physician from the University of Lille in France working at the French reference centre for von Willebrand disease, outlined precisely these initial thoughts. In fact, it clearly appears that VWD has a different prevalence depending on the country in which the disease is diagnosed. For instance, some countries such as France and Italy have a low prevalence while the United Kingdom and Spain have quite a high prevalence. When looking at global figures from the World Federation of Hemophilia (WFH), however, it seems that VWD is generally under-diagnosed. Nonetheless, physicians are noticing a diagnosis paradigm, which consists of under-diagnosis in developing countries and of perhaps over-diagnosis in developed countries. The lack of diagnosis in developing countries seems to be primarily due to lack of diagnosis equipment and expertise. Furthermore, these countries also experience a lack of proper medical treatment and patient support services such as genetic counselling. In developed countries, the over-diagnosis may be linked to identifying genetic defects, which may not necessarily result in bleeds. In fact, amongst all different types of VWD it appears that the types with the worst bleeding scores are VWD type 2A, 2B and 3.

Some of the challenges that will be faced in the future treatment of severe VWD include the management of haemarthrosis (bleeding into joint spaces), the risk of allo-antibodies (inhibitors) in VWD type 3 following exposure to VWF concentrates and managing gastro-intestinal (GI) bleeds.

Participants asked why in France only patients with VWD type 1 and VWF antigen levels below 30 international units (IU)/dl are included in the national registry. This question regarded the existence of national variations and the lack of general agreed-upon levels. Dr Augusto Federici from Milan explained that this was a matter of choice regarding where to put a limit and in the particular case of France the limit was at 30 IU for patients with VWD type 1. He continued to say that in Italy and other countries other criteria also come into play such as the presence of family members and/or a family history. These additional factors can indicate that the patient has VWD. The same situation is also noted in the Netherlands where patients are entered into the national registry only if they have below 30 IU of VWF antigens. This is a grey zone that should be constantly re-evaluated. In fact, in some instances it is perhaps more favourable not to be diagnosed as diagnosis may have a negative effect on health insurance premiums, life style restrictions and increased litigations. Dr Federici underscored that it was important to make the right diagnosis following the correct criteria - otherwise there is a risk of over- or under-diagnosis.

Living with VWD: a personal account

The next presenter was Ms Baiba Ziemele, President of the Latvijas Hemofilija Biedrība (the Latvian Haemophilia Association). Ms Ziemele gave an emotional account of what it was like to grow up and live with VWD in a country with limited means and expertise to diagnose and treat the condition.

She said that while her father was growing up in Latvia, which at the time was still part of the Union of Soviet Socialist Republics (USSR), he knew he had a bleeding disorder but physicians in the country could not determine what it was. Her father was also unaware that this condition could be transmitted to his children and, to this day, Ms Ziemele still does not have a definitive diagnosis for what type of VWD she is suffering from and this is due to the lack of equipment and expertise in her country. Living with VWD has a great impact on Ms Ziemele's daily life and life choices. For instance, she has decided not to have children as Latvia does not have the facilities to care for pregnancies and deliveries of women with VWD. Patients in Latvia are also faced with issues of reimbursement, which means that there is not enough treatment available for patients. This situation was further impacted by the financial crisis, which resulted in a number of patients having their treatment regimen reduced – though luckily this situation is now improving. Finally, in Latvia there is no data for the paediatric population, as the major children's hospitals do not have a registry in place. In short, the current needs for VWD patients in her country include the need to improve diagnosis through better equipment and expertise, develop a set of VWD guidelines, develop awareness campaigns and ensure reimbursement of treatments such as tranexamic acid and VWF concentrate.

Prof Giangrande was struck by the lack of simple medication such as tranexamic acid, which is not very expensive to procure. Dr Federici suggested that Latvia does not need to develop expertise of its own, if this is too difficult, but that it could just set up a twinning with neighbouring countries such as Finland to facilitate the diagnosis of genotypes.

Prophylaxis in VWD

The next presentation was from Dr Susan Halimeh, a treator at the Medical Thrombosis and Haemophilia Treatment Centre in Duisburg, Germany. In her presentation, she gave a brief overview of the disease and the treatment options available as well as the definition of prophylaxis for VWD and the potential indications for when prophylaxis should be started.

VWD is the most frequent congenital bleeding disorder and it is caused by either a reduced or defective production of VWF or a dysfunction of VWF release. There are three main types of VWD with different phenotypes ranging from mild to severe. To determine a patient's phenotype one looks at his/her medical and family history as well as at the results of a bleeding questionnaire that examines general and menstrual bleeds. This will determine a bleeding score for each patient.

In general, in VWD there is a dual defect where both primary and secondary haemostasis are affected by 1) the dysfunction of platelet adhesion and 2) the reduction of factor VIII activity in plasma. The therapeutic options should correct both defects. Depending on the VWD type and the type of bleeding there will be diverse forms of recommended treatments ranging from Desmopressin for acute bleeding and surgery, to antifibrinolytics or oestrogens for menorrhagia, and VWF/ FVIII concentrate for all types of bleeds including joint bleeds.

Dr Halimeh then proceeded to present a short literature review and main findings on the indications for when to start prophylaxis for VWD. In short, prophylaxis with VWF/ FVIII concentrate should be started if there is a contraindication for Desmopressin and if the patient experiences clinically relevant bleeding while 'on demand' treatment (such as recurring bleeds from nose and mouth, joint/muscular bleeding, menorrhagia, GI bleeds and persistent anaemia). From various studies, it appears that patients in the cohort benefited from long-term prophylaxis and that the quality of life in terms of bleeding frequencies, bleeding scores, levels of haemoglobin, VWF and FVIII were improved. For a study using Wilate[®], there was no allergic reaction or inhibitor development.

Dr Halimeh concluded by saying that the decision of whether or not to introduce prophylaxis should only be made after a personal conversation between doctor and patient. From the presentation, it appears that unlike for haemophilia, it remains unclear *how* to proceed with prophylaxis for VWD patients and that at the moment, treatment is tailored to each patient depending on their particular case.

Prof Flora Peyvandi, a member of the EHC MAG, asked how Dr Halimeh managed to get access to prophylaxis treatment for her patients. In fact, despite good results in terms of trough levels and the positive results for haemarthrosis, treatment remains very expensive and for this reason prophylaxis is difficult to attain. Dr Halimeh explained that she personally meets with the insurance company to make the case for each individual patient. This is done with a comprehensive file for each patient including bleeding scores. If the insurance company agrees to cover prophylactic treatment then she has to give a quarterly report on the patient's evolution. This is an incredibly time-consuming activity, however it is, in Dr Halimeh's opinion, worth it.

Prof Angelika Batorova, also a member of the EHC MAG, asked if the use of prophylaxis can avoid the additional use of hormonal treatment, in particular in cases where patients experience menorrhagia and ovulatory bleeds. Dr Halimeh replied that the majority of patients suffering from menorrhagia can be managed with tranexamic acid. A smaller number is treated with the contraceptive pill and a minority with ovulatory bleeds is managed with a combination of tranexamic acid and VWF concentrate. The ovulation is determined by the temperature method.

Combined Factor VIII/ VWF versus recombinant VWF

Prof Pier Mannuccio Mannucci from the hospital Ca Grande in Milan, Italy, gave a presentation on the use of FVIII/VWF concentrate versus recombinant VWF. He proceeded to briefly outline the specificities of the disease as these were also previously outlined by Dr Halimeh. Prof Mannucci then gave a short overview of the available treatments, namely autologous replacement therapy (desmopressin), exogenous replacement therapy (FVIII-VWF concentrate and VWF-only concentrate) and adjuvant treatments (antifibrinolytic amino acids and platelet concentrates). He then reviewed each treatment and explained in which instances these treatments should be used.

The advantages of desmopressin (a synthetic derivative of the antidiuretic hormone) are primarily the ease of production, the low costs and the avoidance of any potential risk of viral infection. However, desmopressin is really only effective in VWD type 1 and sometimes in type 2N. This treatment should not be used in case of poor absolute response to the test dose (as would be the case for severe type 1, 2 and 3). Also, if there is a prediction of prolonged treatment, its use may result in a risk of tachyphylaxis (an acute decrease in the response to a drug after its administration). In these instances FVIII/VWF should be preferred.

Exogenous replacement therapy includes treatments such as FVIII-VWF concentrates and VWF-only concentrates, both plasma-derived and recombinant. Nowadays a combination of FVIII and VWF is preferred for surgeries, spontaneous bleeding episodes and delivery. On the other hand, possible indications for VWF-only concentrates include elective major surgeries, particularly when repeated infusions are foreseen in patients at high risk of thrombosis such as older patients, patients undergoing cancer-related and orthopaedic surgery. Other indications included long-term secondary prophylaxis for patients with target joints, recurring GI bleeding and recurrent epistaxis (nose bleeds) in children.

In conclusion, current treatments are satisfactory and the development of gene therapy seems unjustified unless it is totally devoid of adverse events. However, more research is needed into the role of prophylaxis in VWD, the control of menorrhagia and the control of recurring GI bleeds.

Role of VWF in preventing inhibitor development and facilitating immune tolerance

The Round Table then moved from the topic of VWD and to the role of VWF in preventing inhibitors. For this topic two speakers gave two different perspectives. Dr Carmen Escuriola-Ettingshausen from the Haemophilia Centre Rhein Main, Germany, gave an overview of current clinical studies while Dr Srinivasa Kaveri from the Centre de Recherche des Cordeliers in Paris, France, provided an overview of the current understanding of VWF mechanisms in preventing inhibitor development and facilitating immune tolerance.

Focus on Clinical Trials Evidence

Dr Escuriola-Ettingshausen started her presentation by explaining that inhibitor development is certainly seen as today's most challenging complication in the treatment of haemophilia. Inhibitor development and elimination are influenced by multiple genetic (such as type and severity of haemophilia, the FVIII gene mutation, the family history of inhibitors, the immunogenotype, the HLA type and the ethnic origin) and exogenous variables (such as age at first exposure, therapy regimen, type of concentrate). At the moment it is known that VWF impacts immunogenicity by masking B-cell epitope on the light chain of FVIII, by preventing internalisation of FVIII by bone marrow dendritic cell and hindering antigen recognition of FVIII.

In her presentation, Dr Escuriola reviewed several studies that look at the rate of inhibitor development in previously untreated patients (PUPs) with severe haemophilia A. The studies looked at different treatments including plasma-derived and recombinant factor replacement therapies as well as factor concentrates of both origins with additional VWF. For all the studies and literature reviews presented, results seem to be conflicting as to which type of treatment is the best to prevent inhibitors and much work remains to be done to fully understand the issue.

Dr Escuriola also looked at the Immune Tolerance Induction (ITI), which is currently seen as the optimal treatment following inhibitor formation. Its benefits include regular FVIII prophylaxis for bleeds and surgery and to prevent bleeds and haemophilic arthropathy and increased quality of life. She pointed out that some variables can influence ITI outcome, including pre-ITI conditions, genetic background as well as ITI therapy regimens. The clinical experience in Germany indicates that ITI has a low success rate with recombinant FVIII while a high success rate was noted when using plasma-derived Factor VIII/VWF concentrates. However, in a comparison of different studies by DiMinno and Coppola (*Blood Transfusion*; 2011), it was noted that plasma-derived factor VIII products produced lower rates of success. Dr Escuriola continued her presentation by reviewing many studies (including ObsITI and RESIST) and concluded that much work remains to be done to determine the best course of action for inhibitor prevention.

Focus on Immunology

Dr Kaveri gave a quick overview of the basic principles of immune response of the body. He explained that in the case of inhibitor development in haemophilia, the body recognises the therapeutic factor VIII as a threat and develops an immune response to it. Dr Kaveri reminded the audience that inhibitor development currently occurs in between five to 30 percent of treated patients, that it inhibits the FVIII activity and that it dramatically increases the total cost of yearly treatment to €200,000.

He also confirmed what Dr Escuriola presented, which is that Immune Tolerance Induction (ITI) is at the moment the only proven strategy for achieving antigen-specific tolerance to FVIII. The ITI treatment protocols may include a low-dose or a high-dose regimen and both plasma-derived and recombinant products are used. The current success rate is estimated to be between 50 and 80%.

Although ITI has been widely used since the 1970s, its mechanisms of action remains largely unknown. It is believed that it induces anti-idiotypic antibodies (Gilles J, *Clin Invest* 1996) and that it eliminates FVIII-specific memory cells, which has been shown in mice (Hausl, *Blood* 2005). Dr Kaveri also reviewed the parameters influencing ITI success and time to success such as age at ITI initiation, interval between inhibitor diagnosis and ITI start, dosing regimen, ITI interruption times, historical peak of inhibitors, bleeding and FVIII product. According to Dr Kaveri, the source of uncertainty surrounding ITI is caused by the fact that ITI studies are based primarily on small cohort studies and retrospective national and international ITI registries studies, which results in a lack of significant statistical evidence. As a result, any potential beneficial role of plasma-derived FVIII over recombinant is often attributed to VWF by default, as VWF is often present in plasma-derived products.

At the moment we know that VWF plays two main roles on FVIII immunogenicity: it prevents the anti-FVIII immune response in PUPs and it facilitates the induction of immune tolerance to FVIII. It also reduces the binding of anti-FVIII immunoglobulin G to FVIII. It furthermore reduces the inhibitory activity of anti-FVIII

IgG in functional coagulation assays and it exerts a protective effect, reducing inhibitor inactivation of FVIII. Dr Kaveri then proceeded to explain the effects of VWF on the complement system. In conclusion, he reiterated what Dr Escuriola had already noted: that current research is insufficient and that additional data is needed.

Prof Paul Giangrande noted that patients affected by severe haemophilia do not lack VWF and therefore it is difficult to understand why additional VWF could make a difference. Dr Kaveri agreed and stated that kinetics play a very important role and that there may be other mechanisms occurring with an increase in VWF.

Prof Flora Peyvandi asked why the VWF linked to the FVIII injected in the body is not also rejected and why inhibitors are not developed in response to VWF. Dr Kaveri answered that this was an excellent question for which there was yet no answer.

Acquired von Willebrand Syndrome

Finally, Dr Augusto Federici from the University Hospital of Milan, Italy, presented on acquired von Willebrand Syndrome (AVWS), an acquired bleeding disorder similar to VWD in terms of VWF activity and bleeding. However AVWS unlike VWD occurs later in life and in individuals with no family history of bleeding. At the moment, there are no large prospective studies available for AVWS and only one single Institution Study showed that 25 out of 260 patients with haematological disorders showed a form of AVWS (Mohri et al, *Blood* 1998; 91:3623-3629). A study from Tiede et al (*Blood* 2011; 117:6777-6785) shows that AVWS is often associated with other haematological and cardiovascular disorders. The same study also proposes a pathway to diagnose AVWS looking at VWF activity at the VWF Ristocetin Cofactor (RCo) Activity and at the level of high molecular weight multimers.

Dr Federici explained that when treating AVWS the aim was to treat the underlying disorder and to manage the acute bleeding. He explained that AVWS could occur following surgery for cancer (in cancers such as Wilms Tumors, Adeno Carcinomas and Malignant Neuroectodermal Tumor). AVWS also can occur in patients with aortic stenosis following surgery. In both cases it is often noted that patients go into complete remission. With regard to the therapeutic approaches, they need to be managed according to the specific condition associated with AVWS. In conclusion, Dr Federici pointed out that patients with AVWS can show severe bleeding requiring intensive therapy. Furthermore, an early and correct diagnosis will improve morbidity and mortality rates. Dr Federici then presented the International Registry on AVWS, which is currently aiming to gather further evidence for this syndrome.

Discussions

Following this last presentation, the chair opened the floor for discussions.

On Diagnosis:

- Participants enquired what were the best methods for testing for VWD. According to the physicians present in the room, the best methods are measuring the VWF levels and looking at the family history. However, in cases of a cardiovascular disorder measuring the collagen binding assays can be a more useful tool. Furthermore, other factors can influence the levels of VWF such as oestrogen effect on endothelial cells and hydroxyethyl starch.
- At the moment, tests are under developments to determine inhibitors in VWD type 3.
- Dr Federici and Prof Mannucci further commented on the diagnosis criteria. They explained that there is quite some discordance on diagnosis criteria, even within Europe. To solve this problem, there is a need for a clinical phenotype and new evidence-based guideline. As a guiding principle, three criteria need to be present for diagnosis:
 - Bleeding history,
 - Family history, and

- Low levels of VWF, and these need to be checked at least three times.

If these criteria are not met, the diagnosis cannot be performed. Physicians should be careful not to over-diagnose as it may have negative repercussions on the price and availability of treatment and insurance premiums.

- Dr Halimeh followed-up on this comment and explained that when she diagnoses a patient, she expresses whether it is clinically relevant or not (e.g. if the patients does not have many bleeds then it is not relevant for surgeries). Perhaps, it is necessary to distinguish between whether or not the diagnosis is clinically relevant and to specify what will be the impact on a patients' life.
- Other participants agreed that there should be some level of flexibility when diagnosing.

On raising awareness:

- Ms Liz Carroll, CEO of the UK Haemophilia Society, presented to the audience the 'Talking Red' campaign, which aims to raise awareness about women with bleeding disorders. She explained that the general public does not understand this issue and so the UK Society felt there was a need to raise awareness on this topic. The Society brought together a group of women to discuss an action plan. For the 'Talking Red' campaign, the Society also worked with the nurses association and developed a series of fact sheets and actions that women can do to cope with bleeding disorders. The Society also developed a media campaign with case studies and disseminated it on TV, Facebook and Twitter. The hope is to build the campaign each year using experiences from previous years and to make it bigger and bigger.

On treatment and prophylaxis:

- Dr Susan Halimeh, who is also a patient with VWD type 3, started prophylaxis four years ago due to severe joint bleeds and menorrhagia. She started a prophylactic treatment three times a week at 2,000 IU and the treatment has been having a good effect on her. In her opinion, prophylaxis is fully justified in cases of menorrhagia and joint bleeds. In fact, menorrhagia could be easily assimilated to a joint bleed.
- Prof Peyvandi commented on the fact that at the moment some VWF products are extremely expensive and cost is a barrier to treatment. In particular, she noted that cost is an issue for physicians who do not have the independence to prescribe the product.
- Prof Barotova explained that three factor concentrates containing VWF are available in Slovakia. In this country, the problem comes from the fact that product cost is based on the content of FVIII. This means that certain products are automatically excluded due to their high cost as they have a higher amount of FVIII. There is no distinction made for products with VWF content and which are aimed at treating VWD.
- Participants from Portugal explained that in their country only a handful of specialists can treat VWD type 3 properly while the majority of doctors do not know how to deal with the condition. These participants noted that they did not need prophylaxis; however in their cases they considered correct treatment during childbirth and GI problems to be essential.
- Other participants from the audience noted that amongst VWD patients, it is essential to make a distinction between patients who are bleeders and those who are not, and who may only need ad hoc treatment during specific interventions.
- A representative from Denmark enquired about hormone treatment. She explained that many VWD female patients are treated with hormones and many are often referred to general practitioners and not even specialists and are automatically prescribed hormonal therapy. This participant noted that patients are put on the contraceptive pill at a very early age. Dr Escuriola noted that strong periods are many women's main problem and said that the first option is to propose contraception. This is sometimes refused in which case the second option is to propose

tranexamic acid as an alternative. There is a need to have a strong collaboration with gynaecologists in order to properly diagnose women with heavy periods and who, due to lack of knowledge and expertise, are automatically treated with contraceptives.

- Prof Peyvandi pointed out that in some patients, hormone therapy is not an option due to cultural and reproductive reasons and that physicians needed to be sensitive to these circumstances.
- Participants seemed to agree that the origin of the treatment (plasma-derived or recombinant) did not seem to make much difference as long as it was safe and effective.

Conclusions

Prof Giangrande concluded the event, which he considered fruitful in terms of exchanges and discussions.

All presentations from the event can be found on the EHC website under: <http://www.ehc.eu/round-table-of-stake-holders/last-round-table.html>

The next EHC Round Table will be held on 1 December 2014 at the European Parliament in Brussels and will be chaired by EHC President, Mr Brian O'Mahony. The topic of this event will be: 'National Haemophilia Councils: from concept to reality.'