

Long-term Prophylaxis in von Willebrand Disease – How Should It Be Given and for Whom?

a report by

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DOI: 10.17925/EOH.2008.02.1.34

Von Willebrand disease (VWD) is a common hereditary bleeding disorder that may affect as many as 1% of the general population.¹ VWD is classified into three major categories based on the type of defect and degree of deficiency of von Willebrand factor (VWF). Type 1 is the most common, affecting approximately 75% of those who are symptomatic with VWD,² with type 2 making up most of the

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remainder. Type 3, the most severe form of VWD, is rare, and is estimated to affect from 0.1 to 5.3 per million population.³ Data summarised from six studies showed that among referred patients, type 1 accounted for approximately 70% of VWD cases, type 2 about 17% and type 3 about 13%.³ An extensive survey among haemophilia centres in Italy reported frequencies of 73, 21 and 6 for VWD types 1, 2 and 3, respectively.⁴ However, estimation of prevalence and classification of type is complicated by a number of clinical and laboratory factors.

Clinically, the leading symptoms in VWD are bleeding, chiefly of the mucosal type (e.g. epistaxis, gingival or gastrointestinal [GI] bleeding) and menorrhagia. In severe forms of VWD with secondary deficiency of factor VIII, spontaneous joint and muscular bleeding resembling that observed in severe haemophilia A may also be observed.

Strategies for treatment vary by type and severity, and include the use of 1-desamino-8-D-arginine vasopressin (DDAVP), antifibrinolytics and replacement therapy. Type 1 VWD is the most responsive to DDAVP, type 2 is generally poorly responsive and type 3 is almost invariably unresponsive.⁵⁻⁸ VWF replacement therapy is indicated for the treatment of type 3 and for those with types 1 and 2 who do not respond to DDAVP. Antifibrinolytic agents can be used as adjuncts to DDAVP or VWF concentrates.⁹

Investigators participating in a survey of 74 treatment centres conducted between 2005 and 2006 reported that approximately 70% of their patients with type 3 VWD had been treated with VWF-containing plasma-derived products in the previous 12 months. Twenty-two per cent were on prophylaxis, but this occurred more commonly in Europe

(28.7%) than in North America (12.2%; $p=0.0004$). The use of prophylaxis for patients with type 1 and type 2 VWD was rare in both regions.¹⁰ The most commonly cited reasons for initiating prophylaxis were joint (40%), epistaxis/oral (23%) and GI bleeding (14%) and menorrhagia (5%).

The rationale for initiating long-term prophylaxis in VWD is that it has been successfully used in severe haemophilia, showing that it is feasible to implement early in life in a home setting and that prevention of bleeding and its consequences is possible.^{11,12} Since joint haemorrhages with development of arthropathy can occur, particularly in type 3 VWD, and frequent mucous membrane bleeds, GI bleeding and menorrhagia can jeopardise quality of life or even be life-threatening, it is logical to consider application of the experience learned in haemophilia to VWD. Data to support this come from a multicentre study conducted in Sweden in a group of 52 subjects with VWF ristocetin co-factor (VWF:RCo) <8% and coagulation factor VIII:C (FVIII:C) <10%.¹³ Thirty-nine were on long-term prophylaxis and 13 were treated on demand. The study showed that those beginning prophylaxis below five years of age had few or no bleeding episodes, and none had clinical signs of arthropathy or reported joint bleeding. Subjects beginning prophylaxis above 15 years of age usually reported a substantial reduction in joint bleeding, but had clinical and radiological signs of joint disease. Reductions in other types of bleeding, including epistaxis, were demonstrated. The investigators concluded that long-term prophylactic treatment in VWD is warranted in the majority of cases with type 3 disease and sometimes, depending on the clinical phenotype, for those with other types.

The VWD Prophylaxis Network (VWD PN) was formed to investigate the role of prophylaxis in clinically severe VWD that is non-responsive to other treatments. The VWD International Prophylaxis (VIP) study is an initiative of the VWD PN. The primary objectives of the VIP study are to:

- study the effect of prophylaxis on bleeding frequency; and
- establish optimal treatment regimens for joint bleeding, GI bleeding, epistaxis and menorrhagia.

The secondary objectives are to:

- determine how quality of life at baseline is related to bleeding history and whether changes in bleeding frequency are associated with changes in quality of life among patients with VWD on prophylaxis;
- identify the frequency of development of inhibitory antibodies to VWF among patients with VWD on prophylaxis;
- study the frequency and indications for hospitalisations among patients with VWD on prophylaxis; and
- evaluate the safety of prophylaxis among patients with VWD.

These objectives are being met through a combination of prospective and retrospective studies.

Prospective Study

The prospective component of the VIP study is a non-randomised multicentre study to investigate the role of prophylaxis for joint bleeding, GI bleeding, epistaxis and menorrhagia. Participants will undergo an escalation of treatment from one to three doses of VWD product per week, similar to the Canadian prophylaxis trial using dose escalation in subjects with haemophilia.¹⁴ Subjects begin on treatment level one and remain on this treatment level for the duration of follow-up (one year), or until they meet the criteria for escalation to level two or three. VWF/FVIII products labelled for VWD are chosen for use at the discretion of the participating investigator.

Study Population

Criteria for inclusion are as follows. In type 1 VWD, patients are eligible if they have a RCo level of $\leq 20\%$ and/or a FVIII:C level $\leq 20\%$ and are DDAVP-non-responsive, which is defined as bleeding episodes not responding satisfactorily to desmopressin or deemed non-responsive *a priori* by the investigator, and provided that bleeding indication criteria are met. Type 2 VWD patients are eligible if they are DDAVP- non-responsive, or type 2B, and provided that bleeding indication criteria are met. In type 3 VWD, all patients are eligible provided that bleeding indication criteria are met.

Subjects are excluded from the prospective study if they:

- have acquired VWD;
- have a history of inhibitory antibodies to VWF; or
- are already on prophylaxis or are receiving factor infusions on a regular basis to prevent or reduce the severity of menorrhagia.

Subjects meeting the entry criteria and having patterns of joint or GI bleeding, epistaxis or menorrhagia as defined below are candidates for the study.

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Bleeding Indication and Escalation Criteria

Joint Bleeding

Inclusion in the joint bleeding study requires documentation of at least two spontaneous bleeding episodes in the same joint in the six months prior to enrolment or three or more spontaneous bleeding episodes in different joints in the six months prior to enrolment. Subjects begin at treatment level one: 50U/RCo/kg once per week. In the event a spontaneous joint bleeding episode occurs while on this regimen, the subject escalates to treatment level two: 50U/RCo/kg twice per week. In the event a spontaneous joint

bleeding episode occurs while on treatment level two, the subject escalates to treatment level three: 50U/RCo/kg three times per week.

Gastrointestinal Bleeding

Inclusion in the GI bleeding study requires a history of two or more severe GI bleeding episodes associated with either a drop in haemoglobin of $\geq 2\text{g/dl}$ or requiring red blood cell transfusion or treatment with VWD concentrate. Subjects begin at treatment level one: 50U/RCo/kg once per week. In the event a severe GI bleeding

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episode occurs while on this regimen, the subject escalates to treatment level two: 50U/RCo/kg twice per week. In the event a severe GI bleeding episode occurs while on treatment level two, the subject escalates to treatment level three: 50U/RCo/kg three times per week.

Epistaxis

Inclusion in the epistaxis study requires a history of three or more bleeding episodes in a six-month period that required treatment with VWD concentrates or red blood cell transfusions. Subjects begin at treatment level one, 50U/RCo/kg once per week, escalating to treatment level two, 50U/RCo/kg twice per week, in the event of an occurrence of breakthrough bleeding requiring intervention or two bleeding events that require treatment with factor replacement. Escalation to treatment level three, 50U/RCo/kg three times per week, occurs in the event of an occurrence of breakthrough bleeding requiring intervention or two bleeding events that require treatment with factor replacement while on treatment level two.

Menorrhagia

Inclusion in the menorrhagia study requires a diagnosis of menorrhagia: a prospectively completed Pictorial Blood Assessment Chart (PBAC)¹⁵ score >185 or treatment with a VWF concentrate for menstrual bleeding on at least one occasion in the year prior to enrolment. Subjects begin at treatment level one: 50U/RCo/kg on day one of menses for two cycles. Menstrual flow is monitored by the PBAC score and if the average pictorial chart score is >185 , the subject escalates to treatment level two: 50U/RCo/kg on days one and two of menses for two cycles. If, while on treatment level two the average pictorial chart score is >185 , the subject escalates to treatment level three: 50U/RCo/kg on days one, two and three of menses.

Study Procedures

Tables of study assessments (see *Table 1*) and laboratory tests (see *Table 2*) are shown on pages 30 and 31, respectively. Visits are required to determine eligibility, at entry, three-month intervals, dose escalation and study termination. A diary is maintained throughout the study to record details about infusions, bleeding episodes and PBAC scores (where applicable).

Table 1: VWD International Prophylaxis Study Schedule of Procedures and Assessments

Type of Assessment	Entry	Interval Visit (Every 3 Months)	Dose Escalation	Termination
Medical and VWD history				
VWD diagnosis	*			
Bleeding history (all sites and predominant)	*			
Bleeding episodes (site, date, cause) in prior year	*			
History of pregnancy outcomes ^a	*			
Treatment history	*			
Hospitalisations in the prior year	*			
Other chronic conditions	*			
Medication use	*			
Physical examination, height and weight and review of systems	*	*	*	*
Physical therapy evaluation ^b	*	*		*
X-rays (elbows, knees, ankles) ^b	*			
Quality of life measurement	*			*
Interval medical history				
Number of bleeding episodes (site, date, cause)		*	*	*
Review of infusions (number, dose, indication)		*	*	*
Hospitalisations, surgical procedures		*	*	*
Other medical events		*	*	*
Medication use		*	*	*
Adverse events		*	*	*

a: For all females, regardless of bleeding indication; b: Only for subjects enrolled in the joint bleeding substudy. Physical therapy evaluations will occur at entry and six-month intervals thereafter.

Outcome Variables

The primary outcome for the study is bleeding associated with VWD. In the study of menorrhagia, the primary outcome is the PBAC score. The long-term orthopaedic outcomes of haemophilia are well described. Joint haemorrhages with development of arthropathy can also occur in VWD, particularly in type 3. In the VIP study, musculoskeletal evaluation is carried out bilaterally on knees, ankles and elbows. Two complementary approaches are used, including a physical therapy evaluation at entry and six-month intervals thereafter, using the World Federation of Haemophilia (WFH) joint physical examination scale (WFH PE) and pain scale.¹⁶ X-ray assessment using the Pettersson classification¹⁷ is performed at entry. A consensus reading of X-rays will be completed centrally by two radiologists.

The Health-related Quality of Life 4 (HRQOL-4)¹⁸ and a visual analogue scale to assess perceived state of health are used. The instrument assesses a person’s sense of wellbeing through four questions on self-rated health, number of recent days when physical health was not good, number of recent days when mental health was not good and number of recent days when activity was limited because of poor physical or mental health. Prospective collection of days missed from school or work due to VWD, product usage, hospitalisations and surgical procedures are collected for use in health economic analyses. All participants enrolled in the prospective study will be included in the safety analysis. Safety issues that arise in this study are brought to the attention of the Data and Safety Monitoring Board (DSMB), which acts as a safety oversight committee for the study.

Analytical Approach

The primary objectives of the prospective study are to study the effect of prophylaxis on bleeding frequency and to establish optimal treatment regimens. The analysis method will use the times until bleeding episodes in a multivariate survival analysis model. The length of time bleed-free on prophylaxis will be compared with the experience in the year prior to enrolment. In addition, we will examine: the relationship between

musculoskeletal outcomes and quality of life; the association between the number of bleeding episodes in the year prior to enrolment and quality of life at entry; changes in bleeding and changes in quality of life over the period of follow-up; and the health economic impact of treatment.

Retrospective Studies

The retrospective studies are being conducted in parallel with the prospective study. The retrospective studies are multicentre studies with the following objectives:

- to examine the effect of prophylaxis on bleeding frequency in patients currently on a prophylactic regimen; and
- to characterise the natural history of GI bleeding in VWD.

Effect of Prophylaxis

The retrospective study of the effect of prophylaxis on bleeding frequency comprises individuals with VWD currently on a prophylactic regimen that was initiated at least six months prior to enrolment. Available records supplemented by interview are used to document or reliably estimate the type and frequency of bleeding episodes prior to and after the initiation of prophylaxis. Other variables including product usage, hospitalisations (reasons, procedures, duration), surgical procedures – and, where applicable, past obstetric history – are collected. Pre-prophylaxis bleeding frequency will be compared with the occurrence of bleeding during the post-prophylaxis follow-up period. The percentage reduction in bleeding rate and the length of time bleed-free during follow-up will be calculated. In addition to the primary analysis, a health economic analysis will be performed. Differences in product consumption and the frequency of surgeries and hospitalisations in each period (before and after prophylaxis) will be compared.

Natural History of Gastrointestinal Bleeding

Data from subjects who have a history of GI bleeding either due to proven angiodysplasia or unexplained by other factors are being collected to

Table 2: VWD International Prophylaxis Study Clinical Laboratory Assessments

Type of Assessment	Entry	Interval Visit (Every 3 months)	If Product Is Switched During Study	Termination
Complete blood count	*	*		*
VWF:RCo ^a	*	*	*	*
VWF:Ag ^b	*		*	
FVIII:C ^a	*	*	*	*
Platelet count (most recent)	*			
ABO blood group ^c	*			
Inhibitory antibodies to VWF ^d	*		*	*

a: Trough and peak levels measured at entry and if a product switch occurs during follow-up; trough levels measured every three months at interval visits and at termination; b: Trough and peak levels; c: From diagnostic laboratory evaluation; d: Batched for processing in central laboratory. VWF:RCo = von Willebrand factor ristocetin cofactor; VWF:Ag = von Willebrand factor antigen; FVIII:C = coagulation factor VIII:C.

document the number of bleeding episodes, management and outcome. Of interest is the interval from the onset of the first documented episode of GI bleeding to the point of discontinuation of follow-up or death. The analysis will be descriptive, characterising the population in terms of diagnosis (definitive versus presumptive diagnosis of angiodysplasia), bleeding frequency and severity, treatment and outcomes.

Study Status

The VIP study currently contains 27 centres in Europe and North America. Many of these are in the process of completing the ethical review process. We believe that the efforts to identify and implement optimal prophylactic treatment regimens for VWD will greatly benefit a substantial proportion of people, especially those with type 3 disease, who are most severely affected. We are actively enrolling treatment centres to participate with us in this effort and encourage investigators who might be interested to contact us or members of the steering committee. For more information email Erik.Berntorp@med.lu.se, Thomas.Abshire@emory.edu or SDonfield@rhoworld.com ■

Acknowledgements

The VIP study is an initiative of the VWD PN, an investigator-initiated study funded through an unrestricted grant provided by CSL Behring, Marburg, Germany. The VIP study has been approved by the Haemophilia and Thrombosis Research Society (HTRS) and the American Thrombosis and Haemostasis Network (ATHN), and is officially recognised by the Von Willebrand Factor Standardisation Committee (SSC) of the International Society of Thrombosis and Haemostasis (ISTH). It is registered at www.ClinicalTrials.gov

The steering committee includes the following members: Erik Berntorp, Principal Investigator, Malmö University Hospital, Malmö, Sweden; Thomas Abshire, Co-Principal Investigator, Aflac Cancer Centre and Blood Disorders Service, Atlanta, Georgia, US; Mayte Álvarez, Unidad de Haemofilia Hospital, Universitario La Paz, Madrid, Spain; Manuel Carcao, Haemophilia Program, Hospital for Sick Children, Toronto, Ontario, Canada; Jorge DiPaola, Mountain States Regional Haemophilia and Thrombosis Centre, Aurora, Colorado, US; Joan Cox Gill, Comprehensive Centre for Bleeding Disorders, The Blood Research Institute, Milwaukee, Wisconsin, US; Sharyne Donfield, Rho Inc., Chapel Hill, North Carolina, US; Augusto Federici, Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, Milan, Italy; Peter Kouides; Mary M Gooley Haemophilia Centre, Rochester, New York, US; Karin Kurnik, Dr von Haunersches-Children’s Hospital, Munich, Germany; Frank Leebeek, Erasmus Medical Centre, Rotterdam, The Netherlands; Stefan Lethagen, Copenhagen Haemophilia Centre, Copenhagen, Denmark; Michael Makris, Royal Hallamshire Hospital, Sheffield, England; Pier Mannucci, Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, Milan, Italy; Prasad Mathew, Ted R Montoya Hemophilia Center, Albuquerque, New Mexico, US; Rochelle Winikoff, Haemophilia Treatment Centre, Hôpital Ste-Justine, Montreal, Québec, Canada.

Safety oversight is provided by Christine Lee, Emeritus Professor of Haemophilia at the University of London and an honorary consultant haematologist at the Oxford Haemophilia Centre, UK; and John Hutter, Professor Emeritus of Pediatrics at the University of Arizona, Tucson, Arizona, US.

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