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IN FOCUS

Prophylaxis escalation in severe von Willebrand disease: a prospective study from the von Willebrand Disease Prophylaxis Network

T. ABSHIRE,* J. COX-GILL,† C. L. KEMPTON,‡§ F. W. G. LEEBEEK,¶ M. CARCAO,** P. KOUIDES,†† S. DONFIELD‡‡ and E. BERNTORP§§

**Blood Research Institute and Departments of Pediatrics and Medicine, Medical College of Wisconsin; †Pediatric Hematology, Medical College of Wisconsin, Comprehensive Center for Bleeding Disorders, BloodCenter of Wisconsin, Milwaukee, WI; ‡Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta and Emory University; §Department of Hematology and Medical Oncology, Emory University, Atlanta, GA, USA; ¶Department of Hematology, Erasmus University Medical Center, Rotterdam, the Netherlands; **Department of Paediatrics, Division of Haematology/Oncology, Hospital for Sick Children, Toronto, ON, Canada; ††Department of Medicine, Rochester General Hospital, Rochester, NY; ‡‡Department of Biostatistics, Rho, Inc., Chapel Hill, NC, USA; and §§ Malmö Centre for Thrombosis and Haemostasis, Skåne University Hospital, Lund University, Malmö, Sweden*

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Summary. *Background:* Treatment of mucosal bleeding (epistaxis, gastrointestinal bleeding, and menorrhagia) and joint bleeding remains problematic in clinically severe von Willebrand disease (VWD). Patients are often unresponsive to treatment (e.g. desmopressin or antifibrinolytic therapy) and may require von Willebrand factor (VWF) replacement therapy. There are little data on the use of prophylaxis in VWD, and none have been applied in a prospective, treatment escalation design. *Objective:* Evaluate the effect of escalating dose prophylaxis in severe VWD. *Methods:* Patients eligible for enrollment in this prospective study included those with type 1 VWD with VW factor activity–ristocetin cofactor ratio $\leq 20\%$ and unresponsive to desmopressin, patients with type 2 VWD not responsive to desmopressin and all subjects with type 2B and type 3 VWD. Entry criteria were strictly defined, as were therapy escalation parameters and clinical data collection. *Results:* Eleven subjects completed the study. Six had type 2A, and five had type 3 VWD. Six patients presented with epistaxis, three with GI bleeding, and two with joint bleeding. Seven had dose escalation above the first level. Among the 10 subjects with evaluable bleeding log data, use of prophylaxis decreased the median annualized bleeding rate from 25 to 6.1 (95% confidence interval of the rate difference: −51.6 to −1.7), and the median annualized bleeding rate was even lower (4.0; 95% confidence interval: −57.5 to −5.3) when the subjects reached their final dosing level. *Conclusion:* This is the first prospective study to demonstrate that prophylaxis with VW factor concentrates is highly effective in reducing mucosal and joint bleeding rates in clinically severe VWD.

Keywords: epistaxis; gastrointestinal hemorrhage; hemarthrosis; prophylaxis; von Willebrand disease.

Introduction

Management of bleeding patterns remains problematic for certain cases of severe von Willebrand disease (VWD). These are chiefly mucosal, such as epistaxis, gastrointestinal (GI) bleeding, and menorrhagia, but can also involve the type of bleeding more commonly observed in moderate hemophilia such as joint hemorrhage. Previous studies have confirmed these bleeding manifestations in VWD [1]. The symptoms may not respond to treatment approaches such as desmopressin, antifibrinolytic therapy, or oral contraceptives, necessitating the use of von Willebrand factor (VWF)-containing plasma-derived products.

Correspondence: Thomas C. Abshire, BloodCenter of Wisconsin and Departments of Pediatrics and Medicine, Blood Research Institute, Medical College of Wisconsin, 638 N 18th St Milwaukee, WI 53201, USA.
Tel.: +1 414 937 6434; fax: +1 414 933 6803.
E-mail: Thomas.Abshire@bcw.edu

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The VWD International Prophylaxis (VIP) Study is an initiative of the multicenter von Willebrand Disease Prophylaxis Network (VWD PN). The goal of the VIP study is to examine the effect of regular replacement therapy as prophylaxis in clinically severe VWD that is unresponsive to other treatment(s).

Prophylaxis is common in the treatment of hemophilia, but there are little data on its use in VWD, with the few retrospective studies all demonstrating a reduction in bleeding rates [2–4]. Recent data from a retrospective study completed by the VWD PN provide strong support for the use of prophylaxis for epistaxis, GI bleeding, menorrhagia, and joint bleeding among those most severely affected [5]. The authors now describe efforts to evaluate the effect of prophylaxis for joint bleeding, GI bleeding, excessive bleeding during menses, and epistaxis in a prospective, treatment escalation study. The objectives of this study were to (i) address the effect of prophylaxis on bleeding frequency in severe VWD and (ii) establish optimal treatment regimens (dose and frequency) for the bleeding indications just noted. This report is the first to prospectively evaluate the use of prophylaxis in VWD.

Methods

Population inclusion

Subjects were required to meet criteria for severe forms of VWD, as well as to demonstrate patterns of bleeding specific to one of the indications under investigation. Patients with type 1 VWD were eligible for participation if the VW factor activity–ristocetin cofactor ratio (VWF:RCo) was $\leq 20\%$ and/or factor VIII (FVIII) $\leq 20\%$; b) the patients were desmopressin non-responsive, defined as occurrence of bleeding episodes not responding satisfactorily to desmopressin, or deemed non-responsive *a priori* by the investigator. Subjects with type 2 VWD of all subtypes were eligible if they were desmopressin non-responsive or deemed non-responsive *a priori* by the investigator. All patients with type 2B and type 3 VWD were eligible. Patients were diagnosed locally at their centers.

Criteria for inclusion by bleeding indication were defined as (i) joint bleeding—documentation of at least two spontaneous bleeding episodes in the same joint without evidence of trauma during the 6 months before enrollment or three or more spontaneous bleeding episodes in different joints in the 6 months before enrollment; (ii) GI bleeding—history of two or more severe GI bleeding episodes with no identifiable cause, associated with either a drop in hemoglobin of ≥ 2 g dL^{-1} or requiring a red blood cell transfusion or treatment with a VWF-containing concentrate; (iii) excessive bleeding during menstruation—a diagnosis of menorrhagia was defined by a prospectively completed Pictorial Blood Assessment Chart (PBAC) score > 185 and normal cervical cytology or requiring use of a VWF-containing concentrate for treatment of excessive menstrual bleeding for at least one menstrual cycle during the prior year; and (iv) epistaxis—defined as three or more bleeding episodes in a 6-month period that required treatment with a VWF-containing concentrate or a red blood cell transfusion.

Criteria for exclusion

Subjects were excluded if they had acquired von Willebrand syndrome, had a history of an inhibitor, were on prophylaxis for > 3 months in the year before enrollment, or had a history of non-compliance. Data were collected between 2008 and 2012. The human subjects committees of collaborating institutions approved the VIP study in compliance with the guidelines of the Declaration of Helsinki. The study is registered at www.ClinicalTrials.gov (NCT00557908).

Treatment escalation

Criteria for escalation were specific to each bleeding indication (Table 1) but, overall, involved one significant breakthrough bleeding episode despite compliant prophylaxis. Subjects entering the study began at treatment level 1: 50 IU VWF:RCo/kg once/week and remained on this dose until meeting the criteria for escalation to level 2: two infusions of 50 IU VWF:RCo/kg/week, or level 3: three infusions of 50 IU VWF:RCo/kg/week.

Clinical data collection

Variables collected included demographics, VWD type, site and frequency of bleeding episodes before, and after, the initiation of prophylaxis. The bleeding history was derived from center records or registries, diaries, and logs. Following enrollment, data related to bleeding episodes and frequency of infusions were recorded in diaries maintained by the subject. Treatment of acute bleeding episodes and management of treatment failure, such as severe breakthrough bleeding not adequately controlled by the dose escalation schedule, were at the discretion of the investigator. The type of product used for prophylaxis was at the discretion of the investigator as well, and the VWF product was not provided as part of the study. The duration of follow-up was 1 year.

Statistical methods

Annualized bleeding rates were calculated for the periods before and during prophylaxis. For the prophylaxis period, annualized bleeding rates were calculated for the total time on prophylaxis and for the time at the final treatment level. A 'paired' approach was used to calculate the change in annualized bleeding rate within individuals by subtracting the number of events that occurred before

Table 1 Criteria for escalation specific to each bleeding indication

Joint Bleeding
Level 1: 50 IU VWF:RCo/kg (rounded up to the nearest vial) once/week. In the event a spontaneous joint bleeding episode occurs while on this regimen, the subject will escalate to the level 2 dose following its resolution
Level 2: 50 IU VWF:RCo/kg (rounded up to the nearest vial) twice/week. In the event a spontaneous joint bleeding episode occurs while on this regimen, the subject will escalate to the level 3 dose following its resolution
Level 3: 50 IU VWF:RCo/kg (rounded up to the nearest vial) three times/week
GI Bleeding
Level 1: 50 IU VWF:RCo/kg (rounded up to the nearest vial) once/week. In the event a severe* GI bleeding episode occurs while on this regimen, the subject will escalate to the level 2 dose following its resolution
Level 2: 50 IU VWF:RCo/kg (rounded up to the nearest vial) twice/week. In the event a severe* GI bleeding episode occurs while on this regimen, the subject will escalate to the level 3 dose following its resolution
Level 3: 50 IU VWF:RCo/kg (rounded up to the nearest vial) three times/week
Menorrhagia
Level 1: 50 IU VWF:RCo/kg (rounded up to the nearest vial) on day 1 of menses for two cycles. Menstrual flow will be monitored by the PBAC score. If the average pictorial chart score is > 185, then the subject will escalate to the level 2 dose
Level 2: 50 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1 and 2 of menses for two cycles. Menstrual flow will be monitored by the PBAC score. If the average pictorial chart score is > 185, then the subject will escalate to the level 3 dose
Level 3: 50 IU VWF:RCo/kg (rounded up to the nearest vial) on days 1, 2, and 3 of menses. Menstrual flow will be monitored by pictorial chart
Epistaxis
Level 1: 50 IU VWF:RCo/kg (rounded up to the nearest vial) once/week. The subject will escalate to the level 2 dose in the event of one occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or two bleeding events that require treatment with factor replacement
Level 2: 50 IU VWF:RCo/kg (rounded up to the nearest vial) twice/week. The subject will escalate to the level 3 dose in the event of one occurrence of breakthrough bleeding requiring intervention such as iron replacement therapy, transfusion, packing, hospitalization; or two bleeding events that require treatment with factor replacement
Level 3: 50 IU VWF:RCo/kg (rounded up to the nearest vial) three times/week

A subject's compliance with the prescribed regimen should be evaluated as part of the treating physician's decision to escalate to the next dose. Specific days of treatment administration will be at the discretion of the investigator, with a goal of optimizing levels of VWF. *Defined as GI bleeding associated with either a drop in hemoglobin of ≥ 2 g dL-1 or requiring RBC transfusion.

prophylaxis from the number of bleeds during prophylaxis. A paired Wilcoxon signed rank test of the differences in the medians was used to compare the bleeding rates. The limited sample size did not permit comparison of bleeding rates by indication for each level of treatment or analysis of timing or patterns of escalation.

Results and discussion

Thirteen subjects were enrolled from seven centers in North America and Europe. Two subjects withdrew from the study immediately after enrollment and are not included in the analysis: one decided not to participate and one had clinical indications for more intensive treatment. Eleven completed the protocol. Sixty-four percent of these were male (seven participants), and 36% were female (four participants). The median age (range) at enrollment was 34.6 (3.1–80.6 years). Participants were predominantly white (63.6%) or of African descent (18.2%). Six had type 2A VWD, and five had type 3.

The primary indications for enrollment among those completing the study were epistaxis (six participants), GI bleeding (three participants), and joint bleeding (two participants). The majority of those with epistaxis were children, while GI bleeding occurred among older participants. There were no patients enrolled for treatment of menorrhagia. As shown in Table 2, seven participants had escalated beyond treatment level 1 by the end of follow-up, and the four patients who remained at the entry level dose and interval were treated for epistaxis. Details of trough FVIII:C and VWF:RCo and final treatment level are provided in Table 3.

Bleeding logs were reviewed for accuracy by center personnel and at the data and statistical coordinating center. Logs for 10 of the 11 participants were usable for the analysis of change in bleeding rates; bleeding episodes and infusions for the 11th participant were too inconsistently reported to be reliable. Before the onset of prophylaxis, the median (IQR) annualized bleeding rate was 25.0 (12.0–51.2). This bleeding frequency decreased to a median (IQR) of 6.1 (3.1–29.0) during prophylaxis ($P = 0.027$); 95% confidence interval (CI) of the rate difference: -51.6 to -1.7. However, the median (IQR) annualized bleeding rate was even lower (4.0, 0–27.7); $P = 0.0098$, CI: -57.5 to -5.3, when comparing the rate before initiation of prophylaxis with that observed during the interval after the participant had reached his/her final treatment level.

This is the first study to demonstrate, in a prospective manner, that prophylaxis with appropriate stepwise dose escalation is beneficial in patients with clinically severe VWD. The number of subjects enrolled in this prospective study was far fewer than planned and too few to achieve one of the study objectives, namely to establish the optimal prophylactic treatment regimen for four common types of bleeding in VWD. Nonetheless, it appears that the first dose level (50 IU VWF:RCo/kg once/week) was effective in the majority of the enrolled patients with epistaxis (four of six subjects). Because most of those treated for epistaxis were younger, once/week dosing for this population may be advantageous. Additionally, two other problematic VWD bleeding conditions, GI and joint bleeding, demonstrated bleed-

Table 2 Final treatment level by VWD type and bleeding indication

Treatment level 1		Treatment level 2		Treatment level 3		Escalated beyond level 3*	
Type	Bleeding indication	Type	Bleeding indication	Type	Bleeding indication	Type	Bleeding indication
2A	Epistaxis	2A	Epistaxis	2A	Epistaxis	2A	GI bleeding
2A	Epistaxis	3	GI bleeding	3	Joint bleeding		
3	Epistaxis	3	Joint bleeding	2A	GI bleeding		
3	Epistaxis						

*Regimen escalated to one infusion (75 IU VWF:RCo/kg) every other day.

Table 3 Trough FVIII:C and VWF: RCo levels at enrollment and final treatment levels

VWD type	Primary indication	Final treatment level	FVIII:C trough (IU dL^{-1})	VWF:RCo trough (IU dL^{-1})
2A	Epistaxis	Level 1	102	< 10
2A	Epistaxis	Level 3	94	< 10
2A	GI bleeding	Every other day	77	51
3	Epistaxis	Level 1	3	< 20
3	Joint bleeding	Level 3	4	< 10
2A	Epistaxis	Level 2	80	17
2A	Epistaxis	Level 1	44	10
3	Epistaxis	Level 1	4	< 5*
2A	GI bleeding	Level 3	47	11
3	Joint bleeding	Level 2	2	< 10*
3	GI bleeding	Level 2	4	< 5

Measurement of trough levels was conducted at enrollment after a washout period of at least 72 h. Values indicated by '' are baseline levels obtained before study enrollment.

ing reduction at a less than maximum dosing level. This is similar to results from another dose and interval treatment escalation study, the Canadian Hemophilia Primary Prophylaxis Study Group [6]. Three patients from the current study required the maximum dosing interval and one required tailored higher dosing and frequency.

The annualized bleeding rate was significantly lower, decreasing from a median of 25.0, before prophylaxis, to 4.0 when regular infusions of VWF concentrate were given, a finding that confirms prior retrospective studies. Additionally, it is important to note that controlled dose escalation achieved significant reduction in bleeding in the overall study group, which suggests that a stepwise approach to treatment intervention can be applied to this clinically severe VWD population.

Data to support prophylaxis in subjects with VWD come from a multicenter population-based study conducted in Sweden in a group of 52 subjects with clinically severe VWD [2]. Thirty-nine of these were on long-term prophylaxis and 13 were treated on-demand. The method of treatment was based on clinical criteria (i.e., patterns of bleeding). Results of the study showed that participants beginning prophylaxis at a young age (< 5 years) had few or no bleeding episodes, and none had clinical signs of arthropathy or ongoing joint bleeding. Older participants beginning prophylaxis at > 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 also demonstrated. The investigators concluded that long-term prophylactic treatment in VWD is warranted in the majority of cases with type 3 disease, and in some cases for those with other VWD variants.

Reports from industry sponsored trials investigating the efficacy of bleed reduction from VWF concentrates have also demonstrated similar results as the study discussed and in the previously noted retrospective studies [7–10]. Similarly, a recent retrospective study from the VWD PN also demonstrated efficacy [5]. In the latter study, prophylaxis had the greatest impact in reducing joint bleeding (~90% reduction), supporting the observations cited earlier [2]. Mucosal bleeding such as epistaxis and GI bleeding also showed a reduction after initiation of prophylaxis but to a lesser extent (50–55%).

There were four major barriers to enrollment, as follows: (i) Lack of optimal candidates for study. Patients with more severe forms of VWD were either already on prophylaxis or, in some cases, bleeding symptoms were not severe or persistent enough for study enrollment. (ii) Dose escalation schedule was not embraced by participating institutions. These investigators expressed a preference for individualizing treatment rather than adhering to a standardized dose and interval schedule. This concern is often cited as one reason for the lack of investigator initiated clinical trials in bleeding disorders but for those subjects enrolled in this study, the efficacy of a stepwise dosing and interval treatment approach was encouraging. (iii) Lack of providing a VWF containing product for study patients. (iv) Lack of insurance coverage for some subjects who were considering prophylaxis. This lagging insurance provider support was evident despite the well known use of prophylaxis in VWD for at least a decade in Europe coupled with the frequent off-label use of VWF/FVIII products for treatment of the clinically severe patients with VWD in the United States.

A strength of this investigation is that it shows that a multicenter, dose-escalation prospective study can be con-

ducted across centers in Europe and North America. Unfortunately, evaluation of so few subjects resulted in insufficient statistical power to meet the primary objective of establishing optimal treatment regimens for the most common bleeding conditions in clinically severe VWD. Nonetheless, we were able to demonstrate a significant effect of prophylaxis in reducing bleeding in the overall cohort. These findings provide support for the use of prophylaxis in the context of treatment escalation in severe VWD and should encourage further investigation.

Addendum

T. Abshire designed research, performed research, interpreted data, wrote the manuscript, and gave final approval of the version to be published. J. Cox-Gill designed research, performed research, and gave critical review of the content. C. L. Kempton performed research and gave critical review of the content. F. W. G. Leebeek designed research, performed research, and gave critical review of the content. M. Carcao designed research, performed research, and gave critical review of the content. P. Kouides designed research, performed research, and gave critical review of the content. S. Donfield designed research, gathered data, analyzed the data, interpreted data, and wrote the manuscript. E. Berntorp designed research, performed research, interpreted data, wrote the manuscript, and gave final approval of the version to be published.

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Disclosure of Conflict of Interests

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