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Von Willebrand Factor for Menorrhagia: A Survey and Literature Review

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Abstract

Background—von Willebrand disease (VWD) is the most common congenital bleeding disorder. In women, menorrhagia is the most common bleeding symptom, and is disabling with iron deficiency anemia, high health cost, and poor quality of life. Current hormonal and non-hormonal therapies are limited by ineffectiveness and intolerance. Few data exist regarding Von Willebrand factor (VWF), typically prescribed when other treatments fail. The lack of effective therapy for menorrhagia remains the greatest unmet healthcare need in women with VWD. Better therapies are needed to treat women with menorrhagia.

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Addendum

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Author Contribution

M. Ragni and N. Machin designed the study, performed the research, analyzed and interpreted the data, and wrote the manuscript. L. Malec and A. James contributed to design of the study, interpreted the data, and critically reviewed the manuscript. C. Kessler, B. Konkle, P. Kouides, A. Neff, and C. Philipp performed the research, interpreted the data, and critically reviewed the manuscript. D. Brambilla interpreted the data and critically reviewed the manuscript. All authors approved the manuscript.

Disclosure

N. Machin reports no conflict of interest.

Methods—We conducted a survey of U.S. hemophilia treatment centers (HTCs) and a literature review using medical subject heading (MeSH) search terms “von Willebrand factor,” “menorrhagia,” and “von Willebrand disease” to assess the use of VWF in menorrhagia. Analysis was by descriptive statistics.

Results—Of 83 surveys distributed to HTC MDs, 20 (24.1%) provided sufficient data for analysis. Of 1,321 women with VWD seen during 2011-2014, 816 (61.8%) had menorrhagia, for which combined oral contraceptives, tranexamic acid, and desmopressin were the most common first-line therapies for menorrhagia, while VWF was third-line therapy reported in 13 women (1.6%). Together with data from 88 women from six published studies, VWF safely reduced menorrhagia in 101 women at a dose of 33-100 IU/kg on day 1-6 of menstrual cycle.

Conclusions—This represents the largest VWD menorrhagia treatment experience to date. VWF safely and effectively reduces menorrhagia in women with VWD. A prospective clinical trial is planned to confirm these findings.

Keywords

menorrhagia; von Willebrand disease; von Willebrand factor; women's health

Introduction

von Willebrand disease (VWD) is the single most common congenital bleeding disorder, occurring in 0.1% of the population [1]. VWD is characterized by deficient or defective von Willebrand factor (VWF), a glycoprotein which promotes platelet adhesion to vessel walls after vessel injury. VWF plays a critical role in platelet adhesion and platelet plug formation during primary hemostasis, and serves as a carrier protein for factor VIII [2]. Deficiency of VWF results in mucosal bleeding in the oropharyngeal, gastrointestinal, and genitourinary tract [1-3], and, among women, menorrhagia is the most common symptom occurring in 80% or more [3-5]. Menorrhagia is associated with significant morbidity including symptomatic iron deficiency anemia, psychological stress, and reduced quality of life, with excess days lost from work, lifestyle disruptions, and increased health care costs [4-8]. Further, the lack of effective treatment for menorrhagia is an unmet health need among women with bleeding disorders [5, 6, 9, 10]. The recommended non-hormonal agent, tranexamic acid (*Lysteda*®, *TA*), is an anti-fibrinolytic agent which reduces menstrual blood loss by 50%, but is limited by nausea [11, 12]. Another non-hormonal agent, desmopressin (DDAVP), which stimulates endothelial release of VWF [3], also reduces menstrual blood loss in 50% [3, 13, 14] but hyponatremia and infusion reactions may complicate its use [13, 15]. Although more convenient, the intranasal form of DDAVP, *Stimate*®, has less potent effect on VWF release [11, 13, 14, 16-19]. Combined oral contraceptives, which stimulate factor VWF and factor VIII synthesis, are effective in 70% [19], but only 35% of women use these agents for menorrhagia [15] because of headaches and hypertension [14, 15, 19]. The levonorgestrel intrauterine system (*Mirena*®) which releases hormone into the endometrial cavity which produces an anti-fibrinolytic effect that reduces blood loss [20], is limited by weight gain and depression in 20% [20]. Recombinant interleukin-11 (*Neumega*®, rhIL-11), reduces menorrhagia in over 70% of patients [21] by increasing platelet VWF mRNA expression and VWF synthesis. While mild, reversible fluid retention was observed in some

subjects [21], rhIL-11 is no longer manufactured because of toxicity at higher doses used in cancer chemotherapy patients.

Plasma-derived VWF concentrate (*Humate-P*®, pdVWF) is prescribed for menorrhagia when the above agents fail [3, 4, 13], but it is costly and requires intravenous administration, and little information is available on its use in menorrhagia. Recombinant VWF (*Vonicog alfa, rVWF*), which is currently under FDA review for treating bleeds in VWD, has higher purity and potency than pdVWF [22], and safely reduces bleeds in severe VWD [23, 24], but few data are available on its use in menorrhagia. Thus, there is a lack of safe, effective treatment for menorrhagia and insufficient data to guide management of menorrhagia in women with VWD.

To meet the goals of Healthy People 2020 to promote safety and prevent complications of blood products [25], we designed a study to determine the feasibility of a prospective, randomized crossover trial to reduce menorrhagia based on a trial concept developed by the Hemophilia and von Willebrand disease Subcommittee of the 2009 National Heart, Lung and Blood Institute (NHLBI) State of the Science (SoS) Symposium [26]. As few data exist on VWF to reduce menorrhagia, we designed a survey to determine current treatment practice in U.S. hemophilia treatment centers (HTCs). Further, to determine the published experience with VWF, including pdVWF and rVWF, in the treatment of menorrhagia, we performed a literature review. The results of the survey and literature review are presented herein.

Methods

Survey

As part of a U34 HL-119582 feasibility study to design a future multicenter trial to reduce menorrhagia in women with VWD, the VWD MINIMIZE Trial, we conducted an 8-question survey, distributed by email to U.S. HTCs, utilizing membership lists of the Centers for Disease Control (CDC), <https://www2a.cdc.gov/ncbddd/htcweb/Main.asp>, and the Hemostasis Thrombosis Research Society of North America (HTRS) via site <http://htrs.org>.

Literature Review

A literature review was performed using PubMed medical subject heading (MeSH) search terms [von Willebrand disease], [menorrhagia], and [von Willebrand factor]. Statistical analysis was by descriptive statistics.

Results

Survey

Of 83 surveys distributed in February 2015 to hemophilia treatment centers (HTCs), 35 HTC MDs responded (42.2%) but only 20 HTC MDs (24.1%) provided sufficient data for analysis (Table 1). Ten of the 15 HTCs (66.6%) with insufficient responses were pediatric HTCs, with none or too few women with VWD to complete the questionnaire. The responding HTC MDs reported a total of 1,321 unique women with type 1 VWD, 18-45 years of age, seen during the 3-year period 2012-2014, of whom 816 (61.8%) had

menorrhagia (Table 1). The most common first-line therapy for menorrhagia among surveyed HTC MDs was COCs, reported by 50.0% of the 20 HTC MDs, followed by the non-hormonal agents, TA in 30.0% and desmopressin (DDAVP) in 20.0%. Overall, including all therapies reported, including first-, second-, and third-line therapies, COCs were prescribed by 90% of the 20 HTC MDs, DDAVP by 85%, TA by 85%, epsilon aminocaproic acid (*Amicar*®) by 25.0%, and the levonorgestrel-releasing intrauterine system (*Mirena*® IUD) by 5.0%. Only 4 HTC MDs (20.0%) reported they prescribed VWF concentrate (VWF) for menorrhagia as third-line therapy after other treatments had failed. They reported a total of 13 women, on whom clinical information was available, received VWF at 50 IU/kg for up to 5 days of menstrual bleeding per cycle, with reduction in menorrhagia in all 13 (100%) with no adverse effects.

Literature review

The literature search identified six published studies in which VWF concentrate was used to treat menorrhagia in women with VWD, including two prospective clinical trials, two retrospective observational trials, and two observational networks [24, 27-31] (Table 2). The studies reviewed reported VWF concentrate use in patients with *any* bleeding symptom, from which VWF use by women with menorrhagia was extracted from these broader studies. Of 355 patients with VWD reported in these studies, 88 (24.8%) were women with type 1, 2, or 3 VWD with menorrhagia treated with VWF. Of these, 84 received plasma-derived VWF (pdVWF), 33-95 IU/kg for 1-6 days/cycle, and 4 received recombinant VWF (rVWF), 39-95 IU/kg for 1-2 days/cycle. Together with the 13 women identified in the survey (above), this represents a total of 101 women who have received VWF for menorrhagia, all of whom had reduction in menstrual blood loss, with no reported adverse events.

Trial Feasibility

Of 20 surveyed HTCs, 16 HTCs (80.0%) indicated they would participate in a phase III trial to reduce menorrhagia comparing rVWF vs. TA, although only 4 HTCs (25.0%) actually currently prescribe VWF for menorrhagia. Barriers to participation in a future phase III trial include insufficient staff at 6 HTCs (33.3%), budget issues at 6 HTCs (33.3%), IRB preparation at 5 HTCs (27.8%), and other issues at 5 HTCs (27.8%), including insufficient patients to enroll at 4 HTCs (22.2%), leading 2 of the HTCs to decline participation in the trial, and patient travel costs at one HTC (6.2%). Barriers to participation were further explored in 30-minute structured interviews with 20 HTC MDs and 20 women with VWD and menorrhagia. Despite the expense and requirement for intravenous access and inability of most subjects to infuse, both patients and MDs found this approach acceptable, given the “lack of response to current therapy,” the “lack of better treatments,” and belief that “replacing the missing VWF will help.” Both MDs and patients were willing to participate, but only with a “nurse to help with infusions.” Neither the MDs nor the patients were willing for study subjects to learn and perform self-infusion for only 1-2 doses for 2 menstrual cycles. Some had concerns about inability to schedule HTC or VNA visit for rVWF infusion on day 1 of menses. The main *patient* concerns were time and travel required for visits, need for a nurse to do infusions, scheduling infusions the same day menses start, missing work, childcare, and pregnancy risk and teratogenic effects if COCs were stopped. The main *MD*

concerns were finding sufficient eligible patients, pregnancy risk, and the time and cost of setting up contracts, and sufficient funding to cover laboratory, IRB and nursing costs.

Trial concept and design

We, therefore, propose a phase III multicenter 24-week trial, the VWDMin trial, to compare rVWF with the current non-hormonal treatment of choice, tranexamic acid (TA), to reduce menorrhagia in women with type 1 VWD. Because randomized trials are challenging to accomplish in rare diseases, we worked with experts in rare disease trial design, and chose a randomized crossover design which allows each woman to serve as her own control and receive each drug. Because rVWF is given intravenously and costs more than TA, we hypothesized that in order to be adopted in clinical practice, rVWF would need to be superior to TA and sufficiently acceptable to study subjects to use it after the trial, in order to justify the higher cost and intravenous route. Using as our primary endpoint, the pictorial blood assessment chart (PBAC), a validated measure of menstrual severity, we estimated rVWF would need to reduce PBAC score by 40 points more than TA [Fig.1]. A sample size of 60 achieves 84% power at a type 1 error rate of 0.05 to reject the null hypothesis of no difference when the true difference between changes in PBAC from baseline between drugs is 40 points. This was inflated to 66, as, based on previous studies of TA in VWD, less than a 10% dropout rate is expected [11]. We identified in our 2015 survey 16 HTCs and subsequently 3 non-surveyed HTCs interested in participating in the trial and enroll a minimum of 1 subject per HTC per year or ~19/yr, or ~75 subjects over 4 years, which is ~6% of the total available patients, thereby achieving the sample size, N=66, to complete this trial in 5 years. Thus, the U34 feasibility study indicates the trial is acceptable to MDs and patients, sufficient sites and potential subjects are available to conduct the trial. To promote participation, self-infusion will not be required per MD and patient preference: instead, rVWF will be given on day 1 (or day 2) of menses per patient choice to allow for scheduling by either the HTC nurse or visiting nurse (VNA). Recruitment will exclude those with past thrombosis or current estrogen use to avoid thrombosis risk. Study visits will be scheduled after each of 2 cycles (1 & 2, and 3 & 4) to minimize time and travel burden, and real-time outcomes will be collected monthly with monitoring by HTC nurses. Finally, travel and nursing costs will be compensated; and central IRB submission will be offered to ease HTC staff effort.

Innovation

The concept we propose is *high-impact*, as it addresses the greatest burden and unmet need in women with VWD, the lack of safe, effective treatment for menorrhagia [5, 6, 9, 10]. The trial is *innovative* as it will evaluate rVWF, which is safe and effective in the treatment of bleeds in VWD, for a *new indication*, treatment of menorrhagia. Though few data are available to guide treatment, our HTC survey and literature review indicate VWF (pdVWF primarily) over a wide range of doses, safely reduce menorrhagia in 95% of women with VWD. With the anticipated licensure of rVWF in late 2015 and its 1.4-fold prolonged half-life and high purity and potency, we *hypothesize* a single dose of rVWF will be superior to TA in reducing menorrhagia. Our randomized crossover design is *innovative* and compelling, as each woman serves as her own control, and the goal of our trial are consistent with Healthy People 2020 objectives to promote safety of existing products [25].

Discussion

This survey and literature review of women with VWD and menorrhagia represent the largest treatment experience with VWF to date. It confirms that COCs are the most common hormonal and TA is the most common non-hormonal first-line therapy prescribed by HTC MDs for menorrhagia, while VWF (pdVWF) is prescribed as a third-line therapy for menorrhagia only after other agents fail. Review of the published studies of VWF used in women with menorrhagia indicates pdVWF reduces menorrhagia in women with VWD with few adverse effects. Our data indicate the *most common* VWF regimen used to treat menorrhagia by HTC MDs is 50 U/kg for up to 5 days, although there is wide variability in dose and frequency prescribed by HTC MDs, 33-100 U/kg over 1-6 days. The four women treated with rVWF were participants in a phase III trial of a new recombinant VWF [24], currently under review by the FDA, and received a median dose of 43 U/kg for 1-2 days for menorrhagia. As compared with pdVWF, rVWF has negligible transmissible agent risk and similar potency, platelet binding, collagen binding, and platelet adhesion [22], suggesting it might be a potential new therapeutic for menorrhagia. Whether the modest 1.4-fold increase in rVWF half-life as compared with pdVWF [24] will allow for once per cycle dosing with extended protection is unknown. The higher purity and specific activity of rVWF as compared with pdVWF may also contribute to greater function [22-24]. Clearly, it will be critical to establish acceptability of rVWF as it requires intravenous infusion and would be anticipated to be more costly than other non-hormonal therapies.

There are a number of limitations of retrospective surveys, including recall bias, selection bias, short follow-up, lack of data verification, and representativeness of a few HTCs to all HTCs. Further, the assessment of menorrhagia by subjective response, while routinely used by gynecologists in practice, is less objective than validated measures of blood loss severity, such as the pictorial blood assessment chart (PBAC) [32], or surrogate markers such as improvement in hematocrit and iron stores, or quality-of-life measures which have been used to assess treatment response to therapy [11, 21]. Finally, while data from surveys and reviews cannot replace clinical trials for determining safety and efficacy of therapeutic agents, they complement existing information and confirm the need for prospective trials of new agents to treat menorrhagia in women with VWD.

Conclusions

Our findings indicate while VWF concentrates are typically prescribed as third-line therapy after other agents have failed, they safely reduce menorrhagia in the majority of women with von Willebrand disease. The optimal dose and duration of therapy, objective quantitation of blood loss reduction, and satisfaction with this more invasive and potentially more expensive therapeutic agent remain to be established. We believe our findings provide support for a prospective, multicenter randomized clinical trial to determine the safety and efficacy of recombinant von Willebrand factor when used with tranexamic acid, the current standard non-hormonal therapy, compared with tranexamic acid alone in reducing menorrhagia in women with von Willebrand disease.

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Figure 1.
Schema for the Von Willebrand Disease Minimize (VWDMin) Trial.

Table 1

Survey of Menorrhagia Treatment Practice in U.S. Hemophilia Treatment Centers

Survey Questions		Number (%)		
No. Women with VWD, 15-45 years (18 HTC's)		1,321		
2014		481 (36.4%)		
2013		433 (32.8%)		
2012		408 (30.9%)		
No. Women with VWD and Menorrhagia (18 HTC's)		816 (61.8%)		
2014		307 (37.6%)		
2013		257 (31.5%)		
2012		252 (30.9%)		
Menorrhagia Treatment (20 HTC's)	<i>1st-line</i>	<i>2nd-line</i>	<i>3^d-Line</i>	
COC	14/20 (70.0%)	2/20 (10.0%)	2/20 (10.0%)	
TA	6/20 (30.00%)	6/20 (30.0%)	5/20 (25.0%)	
DDAVP	4/20 (20.0%)	8/20 (40.0%)	5/20 (25.0%)	
<i>Mirena</i> ®	0/20 (0%)	0/20 (0%)	1/20 (5.0%)	
<i>Amicar</i> ®	0/20 (0%)	2/20 (10.0%)	3/20 (15.0%)	
VWF concentrate	0/20 (0%)	0/20 (0%)	4/20 (20.0%)	
Mean Percentage Unable to Tolerate Hormones (18 HTC's)		32.5% (0-50%)		
Barriers to Participation (18 HTC's)				
Insufficient Nursing Staff		6/18 (33.3%)		
Budget Issues		6/18 (33.3%)		
Insufficient Resources for IRB preparation		5/18 (27.8%)		
Other		5/18 (27.8%)		
Insufficient Patients		4/18 (22.2%)		
Patient Travel Costs		1/18 (5.5%)		
Willingness to Participate in VWDMin Trial (16 HTC's)		16/18 (88.9%)		
Estimate of Potential Number Subjects Participating in Trial (16 HTC's)		4-5/ HTC over 4-year trial		
1-2 over 4-year study		2/16 (12.5%)		
3-4 over 4-year study		7/16 (43.7%)		
5-6 over 4-year study		4/16 (25.0%)		
7-8 over 4-year study		2/16 (12.5%)		
9-10 over 4-year study		1/16 (6.2%)		

COCs is combined oral contraceptives; TA is tranexamic acid; DDAVP is desmopressin (intravenous or intranasal); *Mirena*® is levonorgestrel intrauterine system; *Amicar*® is epsilon aminocaproic acid.

Table 2

Literature Review and Survey: VWF in Women with von Willebrand Disease and Menorrhagia

Study/ Survey	Type Study	No. VWD Subjects In Study	No. VWD with Menorrhagia VWF-Treated	Type VWD	VWF Product	VWF Dose Mean (Range) IU/kg	VWF Dose Frequency per Cycle	Percent Bleed Reduction *	Adverse Events [†]
Literature Review									
Abshire et al ²⁷	Retrospective VWD Network	N = 59	N = 4	NA	pdVWF	39 (38-40) IU/kg	3/week	100%	NA
Batty et al ²⁸	Retrospective Single-Center Study	N = 54	N = 1	1, 2, 3	pdVWF	45 (40-50) IU/kg	1 days	100%	Allergic reaction [‡]
Berntorp et al ²⁹	Prospective Observational Studies (n=4)	N = 44	N = 8	1, 3	pdVWF	36 (36±12) IU/kg	1-4 days	97%	No VTE
Holm et al ³⁰	Retrospective Study (n=1); Prospective Trial (n=1)	N = 105	N = 9	1, 2, 3	pdVWF	44 (39-50) IU/kg	3/week	100%	NA
Gill et al ²⁴	Prospective Phase III Trial	N = 22	N = 4	1, 2, 3	rVWF	43 (39-95) IU/kg	1-2 days	100%	NA
Miesbach et al ³¹	Retrospective Observational Study	N = 71	N = 62	1, 2, 3	pdVWF	50 (33-100) IU/kg	1-6 days	95%	VTE [‡]
SUBTOTAL		N = 335	N = 88	1, 2, 3	VWF	43 (33-100) IU/kg	1 – 6 days	95-100%	None
Survey									
Ragni et al (this survey)	Retrospective Survey	- **	N = 13	1, 2, 3	pdVWF	50 U/kg [‡]	5 days	100%	None
TOTAL			N = 101	1, 2, 3	VWF	43 (33-100) IU/kg	1-6 days	95-100%	None

* Bleed reduction in the clinical studies overall ranged from 95-100%, which included menstrual bleed reduction, with all subjects reporting menstrual bleed reduction (100%). All surveyed subjects using VWF reported menstrual bleed reduction (100%). Note that all menstrual bleeding responded to treatment with VWF (pdVWF or rVWF).

[†] Adverse events were reported in VWD subjects overall, but none occurred in women with menorrhagia.

[‡] The dose and duration were based on available data from four subjects. NA = unavailable; VTE = venous thromboembolism; pd VWF = plasma-derived VWF; rVWF = recombinant VWF.

** Note that all subjects in the survey were women with menorrhagia, 13 of whom had clinical information regarding VWF treatment.