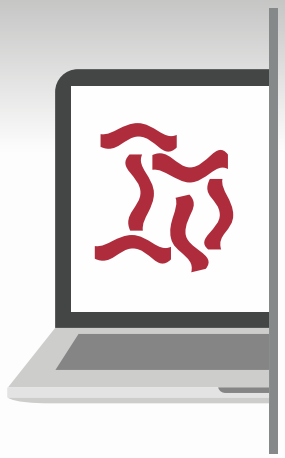
REAL FUNDACIÓN VICTORIA EUGENIA



CICLO DE SEMINARIOS ONLINE

ACTUALIZACIONES EN HEMOFILIA Y OTRAS COAGULOPATÍAS

Visión multidisciplinar

"LA ENFERMEDAD DE VON WILLEBRAND: MANEJO DE LAS CIRUGÍAS Y PROFILAXIS"

6noviembre2024 / 18:00horas

CON LA COLABORACIÓN DE:

octapharma®

SEMINARIO ONLINE:
“La enfermedad de Von Willebrand: manejo de las cirugías y profilaxis”

EDITA:
Real Fundación Victoria Eugenia

Maquetación: A Imprenta Ourense S.L.

www.rfve.es

ISBN: 978-84-09-67944-7

ÍNDICE

REAL FUNDACIÓN VICTORIA EUGENIA

Introducción

SEMINARIO SOBRE ENFERMEDAD DE VON WILLEBRAND
"La enfermedad de Von Willebrand: Manejo de las cirugías y profilaxis."

Mariana Canaro Hirnyk[1]

La enfermedad de von Willebrand (EVW) es un trastorno hemorrágico genético causado por una deficiencia o disfunción del factor de von Willebrand (FvW), una proteína esencial para la coagulación de la sangre.

El objetivo del tratamiento de la VWD es revertir el doble defecto hemostático resultante de la expresión anormal o reducida del VWF y la deficiencia concomitante del factor VIII (FVIII).

El tratamiento consiste en el control de las hemorragias con antifibrinolíticos, desmopresina o concentrados de factor VIII/VW profilaxis a corto plazo (por ejemplo, para intervenciones quirúrgicas o procedimientos invasivos) y a largo plazo.

Ante un procedimiento quirúrgico se requiere una planificación con antelación y una gestión cuidadosa durante el postoperatorio para evitar un sangrado excesivo.

Con un tratamiento individualizado, muchos pacientes con VWD pueden someterse con seguridad a una intervención quirúrgica con mínimas complicaciones y es crucial una estrecha colaboración entre los equipos quirúrgicos y hematológicos para obtener resultados satisfactorios.

En relación al tratamiento de profilaxis, en la enfermedad de Von Willebrand (EVW) el objetivo al igual que en la hemofilia, es prevenir los episodios hemorrágicos, sobre todo en las formas graves de la enfermedad o que se someten a procedimientos invasivos.

La estrategia depende del tipo y la gravedad de la enfermedad, siendo los pacientes con el tipo 3 (deficiencia grave del FvW) los que requieren profilaxis con mayor frecuencia lo que implica la infusión regular de concentrados de FVIII/FVW con frecuencias de 1 a 2 veces por semana para mantener unos niveles de coagulación adecuados.

La profilaxis a largo plazo suele recomendarse a quienes tienen antecedentes de hemorragias graves recurrentes, menorragia en

1. Médico adjunta de la Sección de Hemostasia y Trombosis, Hospital Universitario Son Espases, Palma de Mallorca.

adolescentes y mujeres fértiles, sangrados articulares o gastrointestinales, para mejorar la calidad de vida y disminuir las complicaciones.

La frecuencia de tratamiento se realiza en forma individualizada según patrones individuales de sangrado, estilo de vida y la eficacia clínica.

Adaptar una profilaxis para cada paciente es un proceso complejo, pero muy eficaz en reducir los sangrados

Los objetivos principales son:

Prevenir los sangrados espontáneos, traumáticos o post-quirúrgicos

Disminuir ingresos al hospital y utilización recursos sanitarios

Disminuir el absentismo escolar y laboral

Evitar el desarrollo de artropatía en niños con EVW tipo 3

Posibilidad de realizar tratamiento en casa y mejorar la calidad de vida de los pacientes

En este seminario, la Dra Ana Marco del Hospital Dr. Balmis de Alicante nos hablará del "Manejo perioperatorio de la enfermedad de von Willebrand."

Y la Dra. Elsa Lopez Ansoar del Hospital Alvaro Cunqueiro de Vigo nos hablará del "Tratamiento profiláctico en enfermedad de Von Willebrand: cuándo y cómo hacerlo. Opciones terapéuticas.

REAL FUNDACIÓN VICTORIA EUGENIA

Manejo perioperatorio de enfermedad de Von Willebrand.

Dra. Ana Marco Rico

Unidad de Hemostasia y Trombosis. Servicio de Hematología y Hemoterapia.
Hospital General Universitario Dr. Balmis, Alicante

Índice de la presentación

- Datos a considerar en paciente con EVW que precisa cirugía
- Terapias disponibles en cirugía y EVW
  - ➔ Antifibrinolíticos, DDVAP, terapia reemplazo
- EVW y cirugía mayor
  - ➔ Profilaxis antitrombótica
- EVW y cirugía menor
- EVW y extracciones dentales/otros procedimientos invasivos
- Parto y hemorragia postparto en EVW
- Conclusiones

Introducción

Enfermedad de Von Willebrand

- Es la diátesis hemorrágica congénita más frecuente
- Prevalencia: 1% de la población general
- Herencia AD y menos frecuentemente AR (tipo 2N y 3)
- Heterogénea, varía en gravedad, predominan formas leves
- Predomina sangrado mucocutáneo
- Forma adquirida (SVWA adquirida)

Ante una cirugía

- Abordaje de EVW ante una cirugía depende de
  - Tipo de EVW
  - Perfil hemorrágico: evaluar score hemorrágico (ISTH BAT)
  - Tipo de cirugía: mayor o menor
  - Nivel basal de FVIII y FVW
- No hay consenso de manejo de terapia de reemplazo
- Recomendaciones basadas en opiniones de expertos
- Guías recomiendan que las cirugías se realicen en centros de referencia

Terapias disponibles en EVW

- Medidas locales
- Antifibrinolíticos
- Desmopresina
- Terapia de reemplazo (plasmáticos y recombinantes)
  - Productos con FVIII y FVW
  - FVW puros

Desmopresina

- Análogo sintético de la vasopresina
  ✓Liberación de FVW y de FVIII del endotelio vascular
  ✓Aumento de adhesión plaquetaria
  ✓ Liberación de activador tisular de plasminógeno
- Dosis: 0,3 µg /kg (vía parenteral)
- ➤Aumento FVW y FVIII entre 2-4 veces el valor basal
- Se administra 30 minutos antes de la cirugía o procedimiento invasivo
- Niveles pico a los 90-120 minutos, mantiene hasta 8-10 horas
- *De elección en mayoría de EVW tipo 1 y en algunos casos EVW tipo 2*

Laffan MA et al. BJH 2014; 167: 453-465
Manual práctico de Hemostasia y Trombosis 2018:65-74

Antifibrinolíticos

- Ácido tranexámico o ácido aminocaproico
  ✓ Se unen de modo competitivo e irreversible a los sitios de unión de la lisina del plasminógeno
  ✓ Disminución de activación de plasminógeno en plasmina
- Ácido tranexámico
  ➤Mejor tolerado
  ➤ Dosis:15-20 mg/kg cada 6-8 horas (iv, oral o tópica)
  ➤ Contraindicado en procedimiento de vía urinaria: riesgo de obstrucción
- Ajuste en caso de insuficiencia renal
- *De elección en cirugías menores y procedimientos invasivos, solo o en terapia adyuvante*

Laffan MA et al. BJH 2014; 167: 453-465
Manual práctico de Hemostasia y Trombosis 2018:65-74

Terapia de reemplazo

Table 1. Average ratios of VWF/FVIII content in plasma-derived concentrates licensed for the therapy of VWD

	VWF:RCo/FVIII:C ratio, IU/dL
Alphanate	0.91
Biostate	2.0
Fandhi	1.04
Haemate P/Voncento	2.45
Immunate	0.90
Wilate	0.90

Table 2. Main comparative features of the therapeutic products containing VWF only

	Production method	
Characteristics	Plasma fractionation	Recombinant technology
Commercial name	Wilfactin/Willfact	Vonvendi/Veywondi
Generic name	Human VWF	Vonicog alfa
Licensing	EMA	FDA and EMA
VWF HMWMs	Deficient	All present
Ultra-large VWF multimers	Absent	Present
VWF:RCo/FVIII:C, IU/dL, ratio	>60	FVIII: only traces

En las cirugías mayores y en algunas cirugías menores (EVW tipo 2B y 3)

Miesbach W et al. EJH 2020; 105;365-377

Enfermedad de von Willebrand y cirugía

- *Cirugía mayor*
  - Hospitalización del paciente
  - Implica riesgo vital
  - Anestesia general
  - Cabeza y cuello, algunas de abdomen, ortopédicas
  - Cirugías potencialmente sangrantes
- *Cirugía menor*
  - Manejo ambulatorio
  - No implica riesgo vital
- *Extracciones dentales y/o procedimientos invasivos*
- *Parto*

En una cirugía mayor: niveles FVIII y FVW

In patients with VWD undergoing major surgery, should the FVIII level be kept at ≥0.50 IU/mL for at least 3 days after surgery, or should the VWF activity level be kept at ≥0.50 IU/mL for at least 3 days after surgery?

Recommendation 4a

The panel *suggests* targeting both FVIII and VWF activity levels of ≥0.50 IU/mL for at least 3 days after surgery (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Recommendation 4b

The panel *suggests against* using only FVIII ≥0.50 IU/mL as a target level for at least 3 days after surgery (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Remarks:

- When it is possible to keep both trough levels at ≥0.50 IU/mL for at least 3 days or as long as clinically indicated after the surgery (instead of choosing only 1), this should be the preferred option.
- The specific target levels should be individualized based on the patient, type of procedure, and bleeding history as well as availability of VWF and FVIII testing.
- The duration of the intervention can vary for specific types of surgeries.

Niveles preIQ FVIII y FVW actividad y hasta 36h postIQ: 80-100 UI/dL

Connell NT et al. Blood Adv 2021; 5: 301-325

Table 2. Summary of outcomes and factor levels in studies that reported information at the procedure level

Outcomes	Study	FVIII levels (IU/mL)		VWF levels (IU/mL)	
		Mean (range)	Median (IQR)	Mean (range)	Median (IQR)
Hemostatic efficacy					
Excellent, 74%; good, 11%; fair, 5%; poor, 11%*	Rugeri et al[19]		1.74 (1.53-2.20)		2.10 (0.87-2.10)
Excellent, 84%; good, 16%†	Borel-Derlon et al[16]		2.40 (1.00-3.14)		0.94 (0.48-1.36)
100%‡	Dunkley et al[17]		1.15 (0.97-1.34)		0.85 (0.67-1.03)
Major bleeding					
5%*	Rugeri et al[19]		1.74 (1.53-2.20)		2.10 (0.87-2.10)
0§	Borel-Derlon et al[16]		2.40 (1.00-3.14)		0.94 (0.48-1.36)
Hgb decreased to ≥1.24 mmol/L and/or RBC transfusion					
6.70%§	Srivastava et al[20]	0.92 (0.82-1.02)		0.41 (0.32-0.50)	
3% RBC transfusion‖	Borel-Derlon et al[16]		2.40 (1.00-3.14)		0.94 (0.48-1.36)
20% RBC transfusion‖	Dunkley et al[17]		1.15 (0.97-1.34)		0.85 (0.67-1.03)
Symptomatic VTE					
0.00%	Rugeri et al[19]		1.74 (1.53-2.20)		2.10 (0.87-2.10)
0%	Srivastava et al[20]	0.92 (0.82-1.02)		0.41 (0.32-0.50)	
Wound infection					
0.00%	Rugeri et al[19]		1.74 (1.53-2.20)		2.10 (0.87-2.10)
Received ≥2 units RBCs					
58.00%¶	Rugeri et al[19]		1.74 (1.53-2.20)		2.10 (0.87-2.10)
Estimated blood loss					
Mean, 427 mL (SD, 70-1500 mL)	Rugeri et al[19]		1.74 (1.53-2.20)		2.10 (0.87-2.10)
Duration of hospitalization					
Mean, 5 days (range, 3-13 days)	Rugeri et al[19]		1.74 (1.53-2.20)		2.10 (0.87-2.10)

Brignardello-Peterson R et al. Blood Adv 2022; 6:121-128

Tratamiento reemplazo en cirugía mayor

- Dosis carga: 40-60 UI/kg
- Dosis mantenimiento: 20-40 UI/kg a 8-24 horas de cirugía, diario
- *Depende de niveles basales, tipo de cirugía y evolución clínica*
- *Mantener nivel valle de FVIII y FVW actividad >50 UI/dL, hasta 10-14 días*
- Otras terapias:
  - Compresión local, medidas soporte, transfusión hemoderivados
  - Acido tranexámico (intravenoso)
  - Desmopresina: utilidad limitada

Miesbach W et al. EJH 2020; 105;365-377

Profilaxis antitrombótica en cirugía mayor

- Se ha descrito casos puntuales de ETEV en pacientes que han precisado terapia de reemplazo
- En contexto de
  - Altos niveles de FVIII (>150-200 UI/dL)
  - Presencia de FRCV
  - Cirugía mayor
- **Recomendaciones tromboprofilaxis**
  - ➤ Cirugía mayor
  - ➤ Administrar heparina si presencia de FRCV (misma pauta que pacientes sin EVW)
  - ➤ Monitorizar FVIII diario

En pacientes de alto riesgo trombótico, valorar concentrados sin FVIII o en baja cantidad FVIII

Franchini M et al. J Thromb Thrombolysis 2009; 28:215-219
Miesbach W et al. EJH 2016; 98:121-127

Otras consideraciones en cirugía mayor

- Coste mantener *FVIII o FVW actividad 50 UI/dL durante 3 días*: 5000-12000 US dólares según peso paciente
- Resultados postoperatorios rápidos: disponibilidad laboratorio hemostasia
- No efectos adversos relevantes
- Casos muy puntuales de trombosis (en FRCV y FVIII >150 UI/dL)
- Pocos sangrados postoperatorios relevantes

Brignardello-Peterson R et al. Blood Adv 2022; 6:121-128
Connell NT et al. Blood Adv 2021; 5: 301-325

En cirugía menor

In patients with VWD undergoing minor surgery or minor invasive procedures, should the VWF level be increased to ≥0.50 IU/mL (with use of either VWF concentrate or desmopressin), should tranexamic acid monotherapy be used, or should combination therapy by increasing the VWF level to ≥0.50 IU/mL (with use of either VWF concentrate or desmopressin) in conjunction with tranexamic acid be used?

Recommendation 5a

In patients undergoing minor surgery or minor invasive procedures, the panel *suggests* increasing VWF activity levels to ≥0.50 IU/mL with desmopressin or factor concentrate with the addition of tranexamic acid over raising VWF levels to ≥0.50 IU/mL with desmopressin or factor concentrate

Objetivo: mantener FVIII de 70 UI/dL y FVW actividad de 50 UI/dL

Recommendation 5b

The panel *suggests* giving tranexamic acid alone over increasing VWF activity levels to ≥0.50 IU/mL with any intervention in patients with type 1 VWD with baseline VWF activity levels of >0.30 IU/mL and a mild bleeding phenotype undergoing minor mucosal procedures (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).

Remarks:

- Individualized therapy plans should consider the variation in bleeding risk for the specific procedure in question. Individualized therapy plans are especially important for patients who may be overtreated when VWF activity is increased to ≥0.50 IU/mL by any therapy and addition of tranexamic acid (eg, those undergoing cutaneous procedures, such as superficial skin biopsy).
- Patients with type 3 VWD will require VWF concentrate to achieve any significant increase in VWF activity levels. Use of desmopressin is contraindicated in this population because of lack of efficacy.
- Many patients with type 2 VWD (including patients with type 2B VWD) will also require treatment with VWF concentrate rather than desmopressin.
- For patients at higher risk of thrombosis, it may be desirable to avoid the combination of extended increased VWF and FVIII levels (>1.50 IU/mL) and extended use of tranexamic acid.
- Dental proceduralists may consider use of local hemostatic measures (eg, gelatin sponges or fibrin glue, tranexamic acid rinse) as part of an individualized procedural plan.

Connell NT et al. Blood Adv 2021; 5: 301-325

Table 3. Summary of findings of RCTs that compared increasing VWF levels to 0.50 IU/mL alone vs increasing VWF levels to 0.50 IU/mL and prescribing TXA for patients with VWD undergoing minor surgery

Outcomes	No. of participants	No. of follow-up RCTs	Certainty of the evidence	GRADE	RR (95% CI)	Anticipated absolute effects: Risk with increasing VWF to 0.50 IU/mL + TXA	Anticipated absolute effects: Difference in risk with increasing VWF level to 0.50 IU/mL
Postoperative bleeding	59	2	⊕◯◯◯	Very low*‡	6.29 (2.12-18.65)	109/1000	547 more per 1000 (116-1826 more)
AEs requiring withdrawal	59	2	⊕⊕◯◯	Low*‡	Not estimable	34/1000	34 fewer per 1000 (34-34 fewer)
Major bleeding requiring transfusion	31	1	⊕⊕◯◯	Low*†	Not estimable	0/1000	0 fewer per 1000 (0-0 fewer)
Postoperative blood loss, mL §	28	1	⊕◯◯◯	Very low*†‖			

Brignardello-Peterson R et al. Blood Adv 2022; 6:121-128

Table 4. Summary of findings of studies in which clinicians increased VWF levels to 0.50 IU/mL in patients with VWD undergoing minor surgery

Outcome	No. of participants	No. of observational studies	Total No. of surgeries	Certainty of the evidence	GRADE	Impact
Bleeding complications: hemorrhagic, postoperative bleeding	278	6	281	⊕◯◯◯	Very low*†	Proportion of surgeries in which there were bleeding complications, 11% (95% CI, 6%-19%).
Hemostasis during surgery: excellent or good; adequate, as judged by clinician	88	3		⊕◯◯◯	Very low*	Proportion of procedures in which hemostasis was judged as appropriate, 98% (95% CI, 91%-99%).
No. of patients with need for additional hemostatic agents (postoperative factor replacement)	13	1		⊕◯◯◯	Very low*‡	Proportion of participants who required postoperative factor replacement, 54% (7 of 13). Proportion who required continuous replacement, 38% (5 of 13).
Hospitalization needed for performing the procedure	13	1		⊕◯◯◯	Very low*	In 1 study in which researchers report outcomes of 13 liver or percutaneous biopsies, all 13 patients had to be hospitalized for the procedure.
No. of patients who needed transfusion	51	3	54	⊕◯◯◯	Very low*§	Proportion of participants who needed transfusions, 2% (95% CI, 0%-50%).
Thrombotic serious AEs	76	3	94	⊕◯◯◯	Very low*	Three studies reported this outcome; no thrombotic events occurred in any of the 3 studies.
No. of patients who developed inhibitors or AEs	39	2		⊕◯◯◯	Very low*†	Proportion of patients who developed inhibitors, 2% (95% CI, 0%-21%).
Several definitions provided for AEs	133	4		⊕◯◯◯	Very low*	Four studies reported AEs; 3 reported no allergic reactions (0 of 28 surgeries), no wound infections (0 of 11 surgeries), and no AEs (0 of 29 surgeries); 1 study reported a vasovagal episode that required hospitalization for observation in 1 of 65 patients.

Brignardello-Peterson R et al. Blood Adv 2022; 6:121-128

Table 3 Efficacy and dosing of VWF concentrates during surgery

Product (reference) (VWF/FVIII)	Wilate® (39) (1 : 1) Prospective	Humate® P (40) (1 : 0.4) Prospective – US	Humate® P (24) (1 : 0.4) Prospective – EU	Wilfactin® (41) (1 : ≤0.1) Prospective
No. of procedures	$n = 57$	$n = 35$	$n = 27$	$n = 108$
Share of surgeries in type 3 patients	59%	37%	24%	45%
Excellent or good efficacy	96%	91%	96.3%	100%
Excellent or good efficacy in paediatrics	10 of 10 (100%)	–	–	11 of 11 (100%) (52)
No. of thrombotic events	None	None	2/27 (7.4%) (Pulmonary embolism, thrombophlebitis of the leg)	None
Median dose [IU VWF:RCo/kg] (severity of procedure)	*Loading:* 39 (minor) 49 (major) *Maintenance:* 22 (minor) 21 (major)	*Loading:* 42.6 (oral surg.) 49.9 (minor) 61.2 (major) *Maintenance:* 24.7 (oral surg.) 36.3 (minor) 39.8 (major)	*Loading:* 62.2 (minor) 66.5 (major) *Maintenance:* 38.9–46.8 (minor) 42.3–46.1 (major)	45.5 (minor and major) + Priming co-administration of FVIII in unscheduled procedures only 12%

Miesbach W et al. EJH 2016; 98:121-127

Resultados en cirugía con FVW recombinantes puros

Another phase 3 study was designed to assess the hemostatic efficacy and safety of vonicog alfa, with or without recombinant FVIII, in patients with severe VWD undergoing elective surgery [5]. Fifteen patients undergoing major ($n = 10$), minor ($n = 4$), or oral ($n = 1$) surgery were treated with recombinant VWF. Overall and intraoperative hemostatic efficacy was excellent (73.3% and 86.7%) or good (26.7% and 13.3%) in all cases. Most of the recombinant VWF infusions (89.4%) were administered alone; hemostatically effective levels of endogenous FVIII were reached within 6 hours and maintained for as long as 72–96 hours [5]. A single case of deep vein thrombosis, possibly treatment-related, was and after surgery. More recent data were obtained in the frame of a French retrospective study evaluating the safety and efficacy of vonicog alfa in 53 patients undergoing 63 surgical procedures [55]. Few infusions and low doses of recombinant VWF effectively prevented bleeding in 97% of the procedures. No adverse events, including thromboembolic

Vonicog alfa tiene indicación para tratamiento a demanda, control y prevención de sangrados durante y después de la cirugía

Peyvandi F et al. JTH 2019; 17:52-62
Desprez D et al. Haemophilia 2021; 27:270-276

Extracciones dentales

- Objetivo: mantener FVIII>40-50 UI/dL y FVW actividad >30 UI/dL durante 12 horas

Opciones

- Dosis única de 30 UI/kg de concentrados FVW/FVIII previo al procedimiento
- DDVAP 0,3 µg/kg 20-30 minutos antes del procedimiento
- Antifibrinolíticos sistémicos y locales

Según tipo de EVW

Franchini M et al. Exp Rev Hematol 2023; 16:871-878

Manejo periquirúrgico: En resumen

Table 1 Product types required depending on the VWD subtype in minor and major surgical procedures (18)

VWD subtype	Minor surgical procedures	Major surgical procedures
Type 1	DDAVP	VWF concentrate
Type 2A/2M	DDAVP	VWF concentrate
Type 2B	VWF concentrate	VWF concentrate
Type 2N	DDAVP	VWF concentrate
Type 3	VWF concentrate	VWF concentrate

Valorar añadir antifibrinolíticos

Table 2 Perisurgical coagulation management in patients with VWD [adapted from (13)]

	Major surgery	Minor surgery
Loading dose IU/dL VWF:RCo	40–60 IU/kg	30–60 IU/kg
Maintenance dose IU/dL VWF:RCo	20–40 IU/kg every 8–24 h	20–40 IU/kg every 12–48 h
Monitoring VWF:RCo and FVIII troughs and peaks	At least daily	At least once
Therapeutic goal	Trough VWF: RCo and FVIII >50 IU/dL for 7–14 d	Trough VWF:RCo and FVIII >50 IU/dL for 3–5 d

Miesbach W et al. EJH 2016; 98:121-127

Table 4 The 'dos' and the 'don'ts' in surgery

'Dos'	'Don'ts'
Close cooperation between the surgical department and the haemophilia centre	Do not use DDAVP in type 2B or type 3 VWD in children <2 yr of age and elderly patients with atherosclerosis
	Do not use DDAVP longer than 3–5 d
Regular assessment (and correction) of haemostasis	Do not forget to control fluid intake (<1 L) for 24 h after DDAVP and to control the natrium level
Consider comorbidities and risk factors for thrombosis before choosing the type of VWF concentrate or DDAVP	Do not use VWF concentrate with high FVIII content for multiple infusions
DDAVP test infusion measuring FVIII:C and VWF:RCo levels at baseline, 1 h (peak) and 4 h (clearance) before clinical use	Do not exceed a FVIII level of 150 IU/dL
For minor surgery, VWF:RCo >50 IU/dL should be adequate (often only one infusion is required)	Do not rely on recovery values derived from presurgical pharmacokinetics
For major surgery, use VWF concentrates with low FVIII or devoid of FVIII and plan repeated infusions	Do not forget anticoagulation, particularly in patients with multiple prothrombotic risk factors
In case of emergency surgery, co-infusion of FVIII with the first infusion of pure VWF concentrate is indicated	Do not forget the benefits of adjunctive treatment

Miesbach W ET AL. EJH 2016; 98:121-127

Riesgo de sangrado durante embarazo

- En **mujeres sanas**
  - Niveles FVIII y FVW aumentan con el embarazo, más altos en tercer trimestre, alcanzando FVIII >100 UI/dL en parto
- En **mujeres con EVW**
  - HPP entre 15-60% según series, también en EVW tipo 1
  - EVW tipo 1:
    - Aumento progresivo de FVIII y FVW, alcanzando >50 UI/dL en 3er trimestre
    - HPP que requiere transfusión de CH en 22%
  - Si niveles basales <20 UI/dL: menor aumento por mutaciones que implican mayor aclaramiento o menor síntesis de FVW

Castaman G et al. EJH 2019; 103:73-79
Lavin M et al. JTH 2022; 20:82-91

Manejo parto en mujeres con EVW

- Evitar parto instrumentado
- Tipo parto según criterios obstétricos
- Riesgo de sangrado es mínimo si FVIII:C y cofactor FVW>50 UI/dL
- Se recomienda monitorizar FVIII:C y cofactor FVW al menos 1 vez en 3er trimestre
- Descenso a niveles basales tras el parto:
  - ➤ Ácido tranexámico 1 g/8h durante 2 semanas previene HPP y es seguro durante lactancia

Castaman G et al. EJH 2019; 103:73-79
Lavin M et al. JTH 2022; 20:82-91

Manejo parto según tipo de EVW

EVW tipo 1

- Si FVIII:C y/o cofactor FVW <30 UI/dL
  - Administración de DDVAP y mantener 3-4 días tras el parto
- Si FVIII:C y/o cofactor FVW entre 30-50 UI/dL
  - Administración de DDVAP similar pero menos infusiones
- Alternativas: concentrado FVIII/FVW 40-60 UI/kg

EVW tipo 2A

- Cofactor FVW suele estar reducido, aunque un leve incremento puede ocurrir
- Precisa concentrado de FVIII/FVW

Castaman G et al. EJH 2019; 103:73-79
Lavin M et al. JTH 2022; 20:82-91

Manejo parto según tipo de EVW

- **EVW tipo 2B**
  - Se agrava la trombocitopenia, dependerá de mutación gen FVW
  - Precisa concentrado de FVIII/FVW en parto y durante 3-5 días
  - Mantener plaquetas >50000
- **EVW tipo 2M**
  - Cofactor FVW <50 UI/dL, FVIII y FVW:ag suben durante embarazo
  - Precisa concentrado de FVIII/FVW en parto y durante 3-5 días
- **EVW tipo 2N**
  - FVIII se normaliza en mujeres portadoras de mutación más frecuente (R854Q): DDVAP si sangrado
  - Si otra mutación: concentrado FVIII/FVW 50 UI/dL en parto y durante 3-5 días
- **EVW tipo 3**
  - No aumento de FVW y FVIII durante embarazo
  - Precisa concentrado de FVIII/FVW, mantener FVIII y FVW >50 UI/dL durante 5-7 días tras el parto
  - Algunas pacientes están en profilaxis previo a embarazo que pueden mantener durante el mismo

✓Valorar profilaxis antitrombótica en cesárea al menos hasta suspender factor
✓Acido tranexámico hasta 10-14 días postparto

Castaman G et al. EJH 2019; 103:73-79
Lavin M et al. JTH 2022; 20:82-91

Conclusiones

- Abordaje multidisciplinar
- *Cirugía mayor*:
  - Concentrados de factor ± antifibrinolíticos
  - Objetivo: mantener cofactor y FVIII >50 UI/dL hasta 14 días postIQ
- *Cirugía menor*
  - DVVAP, concentrados factor en tipo 2B y 3
  - Objetivo: mantener cofactor y FVIII >50 UI/dL hasta 3 días postIQ
- Administración de concentrados de FVW puro o baja cantidad de FVIII sobre todo en pacientes de alto riesgo trombótico
- *Parto*
  - DDVAP (tipo 1) y concentrado FVIII/FVW durante parto y 3-5 días
  - Ácido tranexámico reduce HPP

BIBLIOGRAFÍA:

1. Laffan MA, Lester W, O´Donnell JM, et al. The diagnosis and management of von Willebrand disease: a United Kingdom Haemophilia Centre Doctors Organization guideline approved by the British Committee for Standards in Haematology. *British J Hematol 2014; 167:453-465.*
2. Manual práctico en Hemostasia y Trombosis 2018: páginas 65-74.
3. Miesbach W. Perioperative management for patients with von WEillebrand disease: defining the optimal approach. *European J Hematol 2020; 105:365-377.*
4. Connell NT, Flood VH, Brignardello-Petersen R, et al. ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. *Blood Advances 2021; 5: 301-325.*
5. Brignardello-Petersen R, El Alayli A, Husainat N, et al. Surgical management of patients with von Willebrand disease: summary of 2 systematic reviews of the literature. *Blood Advances 2023; 6:121-128.*
6. Franchini M, Targher G, Montgnana M, Lippi G. Antithrombotic prophylaxis in patients with von Willebrand disease undergoing major surgery: when is it necessary? *J Thromb Thrombolysis 2009; 28: 215-219.*
7. Miesbach W, Berntorp E. Von Willebrand disease: the ´Dos´and ´Don´ts´ in surgery. *European J Hematol 2016; 98:121-127.*
8. Peyvandi F, Mamaev A, Wang JD, et al. Phase 3 study of recombinant von Willebrand factor in patients with severe von Willebrand disease who are undergoing elective surgery. *J Thromb Haemostasis 2019; 17:52-62.*
9. Desprez D, Drillaud N, Flaujac C, et al. Efficacy and safety of a recombinant Von Willebrand Factor treatment in patients with inherited Von Willebrand disease requiring surgical procedures. *Haemophilia 2021; 27:270-276.*
10. Franchini M, Focosi D. Targeting von Willebrand disease: the current status and future directions of management therapies. *Expert Review Hematology 2023; 11:871-878.*
11. Castaman G, James PD. Pregnancy and delivery in women with von Willebrand disease. *European J Hematol 2019; 103:73-79.*
12. Lavin M, Sánchez-Luceros A, Kouides P, et al. *J Thromb Haemostasis 2022; 20:82-91.*

REAL FUNDACIÓN VICTORIA EUGENIA

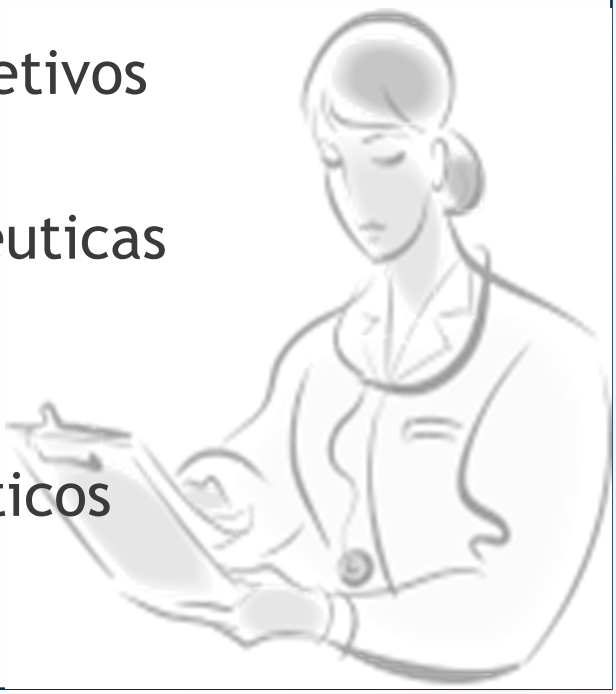
Tratamiento profiláctico en enfermedad de Von Willebrand: cuándo y cómo hacerlo. Opciones terapéuticas.

Dra. Mª Elsa López Ansoar

Servicio de Hematología y Hemoterapia del
Complexo Hospitalario Universitario Álvaro Cunqueiro de Vigo.

AGENDA DE TRABAJO

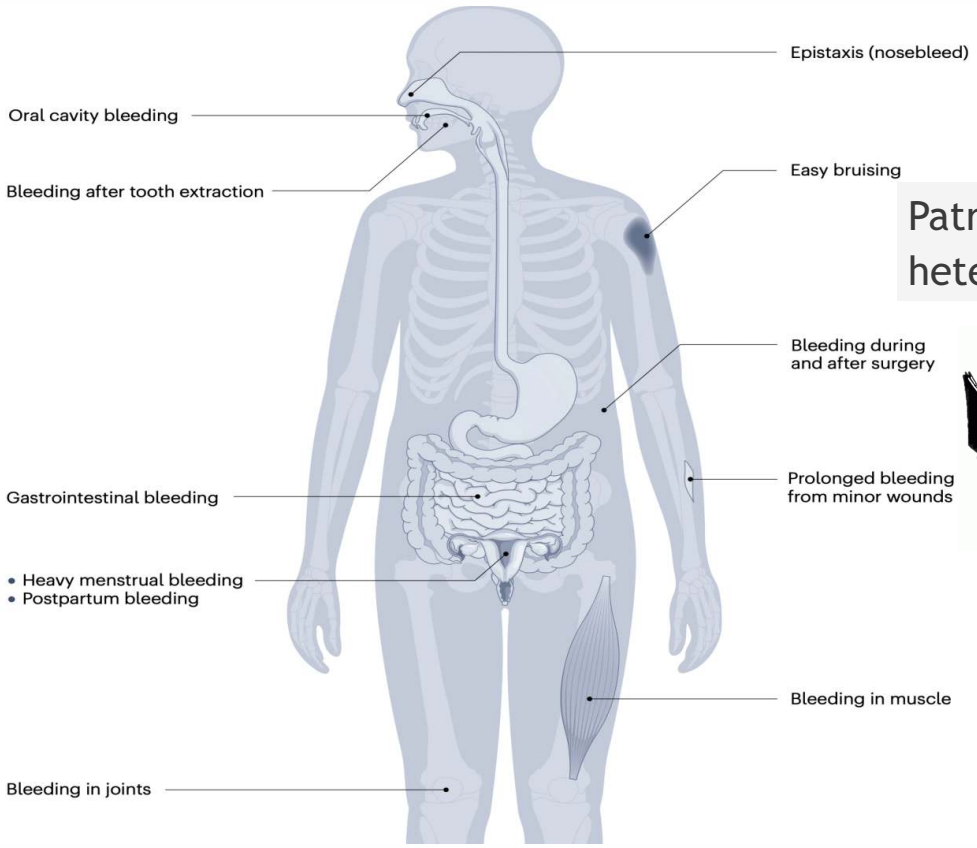
- ❑ Definición y objetivos
- ❑ Opciones terapéuticas
- ❑ Esquemas prácticos



Periodos continuados de tratamiento de al menos 3 a 6 meses con factor de VW al menos una vez por semana

OBJETIVO :DISMINUCIÓN O PREVENCIÓN DE LOS EVENTOS DE SANGRADO

Administración regular durante las menstruaciones en mujeres



Patrón de sangrado heterogéneo

ISTH International Society on Thrombosis and Haemostasis | NATIONAL HEMOPHILIA FOUNDATION for all bleeding disorders | FMH FÉDÉRATION MONDIALE DE L'HÉMOPHILIE WORLD FEDERATION OF HEMOPHILIA FEDERACIÓN MUNDIAL DE HEMOFILIA

Guías 2021 de ASH, ISTH, NHF, FMH para el tratamiento de la enfermedad de Von Willebrand

Profilaxis

Received: 15 August 2022 | Revised: 28 November 2022 | Accepted: 30 November 2022

https://doi.org/10.1016/j.jtha.2022.11.042

JTH IN CLINIC

Beyond the guidelines: how we approach challenging scenarios in the diagnosis and management of von Willebrand disease

Mouhamed Yazan Abou-Ismail[1] | Paula D. James[2] | Veronica H. Flood[3] | Nathan T. Connell[4]

Guías 2021 de ASH, ISTH, NHF, FMH para el tratamiento de la enfermedad de Von Willebrand

Recomendaciones

Profilaxis

RECOMENDACIÓN 1

En el caso de pacientes con EVW y un historial de hemorragias graves y frecuentes, el panel de las guías *sugiere* usar profilaxis a largo plazo en lugar de no usar profilaxis (recomendación condicional basada en una baja certeza en las pruebas científicas de los efectos ⊕⊕◯◯).

Observaciones

- Los síntomas hemorrágicos y la necesidad de la profilaxis deberían valorarse periódicamente.

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Translating the success of prophylaxis in haemophilia to von Willebrand disease

Wolfgang Miesbach [a,*], Erik Berntorp [b]

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Review Article

Translating the success of prophylaxis in haemophilia to von Willebrand disease

Wolfgang Miesbach [a,*], Erik Berntorp [b]

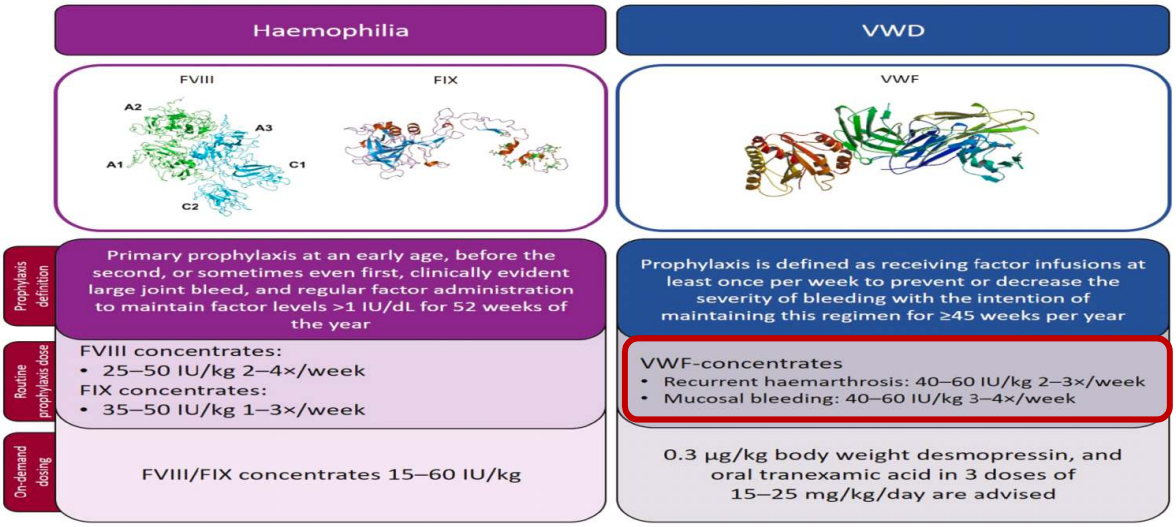


Fig. 1. Current treatment approaches† in patients with haemophilia and VWD [1,49,51,52].
FIX, factor IX; FVIII, factor VIII; VWD, von Willebrand disease; VWF, von Willebrand factor.
†Doses based on current guidelines for haemophilia and vary depending on disease severity and product; newer products have meant dosing frequency can be reduced further than those stated above while maintaining sufficient factor levels.

2021

Therapeutic Advances in Hematology

Prophylactic management of patients with von Willebrand disease

Massimo Franchini, Omid Seidizadeh and Pier Mannuccio Mannucci

Ther Adv Hematol

2021, Vol. 12: 1–12

DOI: 10.1177/20406207211064064

***Abstract*:** Von Willebrand disease, the most common inherited bleeding disorder that affects both males and females, is due to quantitative or qualitative defects of the multimeric glycoprotein von Willebrand factor, which cause mucous membrane bleeding but also soft tissue bleeding owing to the secondary deficiency of factor VIII. The aim of treatment is to correct this dual defect of hemostasis. In addition to the episodic management of bleeding episodes, therapy includes their short- or long-term prevention. Short-term prophylaxis is mainly warranted in order to provide effective hemostatic coverage to patients undergoing surgery or invasive procedures and to affected women at the time of delivery or during menstruations associated with excessive bleeding. The aim of long-term prophylaxis is to prevent bleeding in particular categories of patients at increased risk of frequent and spontaneous bleeding in the joints, nose, and gastrointestinal tract.

Evidencia científica objetiva disminución de tasa de sangrado

Ther Adv Hematol

2021, Vol. 12: 1–12

DOI: 10.1177/20406207211064064

Author	Patients (n)	Median age at start of prophylaxis (range)	VWD types	Median FVIII doses (range)	Indication (*n*)	Main results
Castaman *et al.*[25]	31	NI	9 type 1, 6 type 2, 16 type 3	30 IU/kg (1–169) 2–3 times weekly	GI and joint bleeding, menorrhagia	Excellent/good responses in 93% of cases
Berntorp and Petrini[53]	35	13 years (1–61)	1 type 1, 6 type 2, 28 type 3	24 IU/kg (12–50) 1–3 times weekly	Mucocutaneous and joint bleeding	Number of bleeds reduced after prophylaxis. No arthropathy in children starting prophylaxis before 5 years of age
Federici[56]	11	NI	1 type 1, 5 type 2, 5 type 3	NI	GI (7) and joint (4) bleeding	Excellent/good responses in 100% of cases. Reduction of annual consumption of VWF/FVIII concentrates, number of transfused blood units and days spent in hospital
Holm *et al.*[59]	105	26 years (1–81)	13 type 1, 38 type 2, 54 type 3	NI	Epistaxis (33%), GI (23%) and joint (23) bleeding	Reduction of ABR was statistically significant for all bleeding indications
Abshire *et al.*[60]	11	34.6 years (3–80.6)	6 type 2, 5 type 3	50 IU/kg 2–3 times weekly*	Epistaxis (6), GI (3) and joint bleeding (3)	Median ABR score decreased from 25.0 (IQR: 12.0–51.2) to 6.1 (IQR: 3.1–29.0)
Abshire *et al.*[62]	59	22.4 years (2.3–77.2)	5 type 1, 20 type 2, 34 type 3	40–60 IU/kg (30–6)* 2–3 times weekly	Epistaxis (13), GI (13) and joint bleeding (12)	Prophylaxis was effective in reducing the association bleeding rate, particularly joint bleeding
Halimeh *et al.*[63]	32	Children: 13 years, adolescent: 7 years, adults: 12 years	4 type 1, 15 type 2, 13 type 3	40 IU/kg (20–47) 2–3 times weekly*	GI and joint bleeding	Recurrent bleeding stopped in 31 patients. Monthly bleeding frequency significant reduced ($p < 0.001$)

ABR, annualized bleeding rate; FVIII, factor VIII; GI, gastrointestinal; IQR, interquartile range; NI, not indicated; VWD, von Willebrand disease.
*VWF:RCo IU/kg.

DOI: 10.1111/hae.14550

REVIEW ARTICLE

Haemophilia WILEY

2022

Outcomes of long-term von Willebrand factor prophylaxis use in von Willebrand disease: A systematic literature review

Abdallah El Alayli[1] | Romina Brignardello Petersen[2] | Nedaa M. Husainat[3] | Mohamad A. Kalot[4] | Yazan Aljabiri[5] | Hani Turkmani[6] | Alec Britt[7] | Hussein El-Khechen[2] | Shaneela Shahid[2,8] | John Roller[9] | Shahrzad Motaghi[2] | Razan Mansour[1] | Alberto Tosetto[10] | Rezan Abdul-Kadir[11] | Michael Laffan[12] | Angela Weyand[13] | Frank W.G. Leebeek[14] | Alice Arapshian[15] | Peter Kouides[16] | Paula James[17] | Nathan T. Connell[18] | Veronica H. Flood[19] | Reem A. Mustafa[20]

[1]Outcomes and Implementation Research Unit, Department of Internal Medicine, University of Kansas Medical Center, Kansas City, Kansas, USA

Haemophilia. 2022;28:373–387.

ABSTRACT

Background: Von Willebrand Disease (VWD) is a common inherited bleeding disorder. Patients with VWD suffering from severe bleeding may benefit from the use of secondary long-term prophylaxis.

Aim: Systematically summarize the evidence on the clinical outcomes of secondary long-term prophylaxis in patients with VWD and severe recurrent bleedings.

Methods: We searched Medline and EMBASE through October 2019 for relevant randomized clinical trials (RCTs) and comparative observational studies (OS) assessing the effects of secondary long-term prophylaxis in patients with VWD. We used Cochrane Risk of Bias (RoB) tool and the RoB for Non-Randomized Studies of interventions (ROBINS-I) tool to assess the quality of the included studies. We conducted random-effects meta-analyses and assessed the certainty of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results: We included 12 studies. Evidence from one placebo controlled RCT suggested that VWD prophylaxis as compared to no prophylaxis reduced the rate of bleeding episodes (Rate ratio [RR], .24; 95% confidence interval [CI], .17–.35; low certainty evidence), and of epistaxis (RR, .38; 95%CI, .21–.67; moderate certainty evidence), and may increase serious adverse events RR 2.73 (95%CI .12–59.57; low certainty). Evidence from four before-and-after studies in which researchers reported comparative data suggested that VWD prophylaxis reduced the rate of bleeding (RR .34; 95%CI, .25–.46; very low certainty evidence).

Conclusion: VWD prophylaxis treatment seems to reduce the risk of spontaneous bleeding, epistaxis, and hospitalizations. More RCTs should be conducted to increase the certainty in these benefits.

Beneficios clínicos de la profilaxis

Hemartros y epistaxis recurrentes como principales motivos para iniciar una profilaxis secundaria

- Disminución de la tasa global de sangrados
- Disminución del número de sangrados espontáneos, de hemartros y de epistaxis
- Niños que inician profilaxis antes de los 5 años de edad no llegaron a presentar hemartros
- Inicios de profilaxis tempranas retrasan la aparición de los primeros eventos de sangrado

Ther Adv Hematol

2021, Vol. 12: 1–12

DOI: 10.1177/20406207211064064

Therapeutic Advances in Hematology 12

Table 4. Main data on long-term prophylaxis with concentrates of von Willebrand factor/factor VIII or von Willebrand factor only products in von Willebrand disease.

Author	Patients (n)	Median age at start of prophylaxis (range)	VWD types	Median FVIII doses (range)	Indication (n)	Main results
Castaman et al.[39]	31	NI	9 type 1, 6 type 2, 16 type 3	30 IU/kg (1–16 IF) 2–3 times weekly	GI and joint bleeding, menorrhagia	Excellent/good responses in 93% of cases
Berntorp and Petrini[33]	35	13 years (1–61)	1 type 1, 6 type 2, 28 type 3	24 IU/kg (12–50) 1–3 times weekly	Mucocutaneous and joint bleeding	Number of bleeds reduced after prophylaxis. No arthropathy in children starting prophylaxis before 5 years of age
Federici[34]	11	NI	1 type 1, 5 type 2, 5 type 3	NI	GI (7) and joint (4) bleeding	Excellent/good responses in 100% of cases. Reduction of annual consumption of VWF:FVIII concentrates, number of transfused blood units and days spent in hospital
Holm et al.[35]	105	26 years (1–81)	13 type 1, 38 type 2, 54 type 3	NI	Epistaxis (33%), GI (23%) and joint (23) bleeding	Reduction of ABR was statistically significant for all bleeding indications
Abshire et al.[40]	11	34.6 years (3–80.6)	6 type 2, 5 type 3	50 IU/kg 2–3 times weekly*	Epistaxis (4), GI (3) and joint bleeding (3)	Median ABR score decreased from 25.0 (IQR: 12.8–51.2) to 6.1 (IQR: 3.1–29.0)
Abshire et al.[42]	59	22.4 years (2.3–77.2)	5 type 1, 20 type 2, 34 type 3	40–60 IU/kg (30–47* 2–3 times weekly	Epistaxis (13), GI (13), and joint bleeding (12)	Prophylaxis was effective in reducing the association bleeding rate, particularly joint bleeding
Halimeh et al.[43]	32	Children: 13 years, adolescent: 7 years, adults: 12 years	4 type 1, 15 type 2, 13 type 3	40 IU/kg (20–47) 2–3 times weekly*	GI and joint bleeding	Recurrent bleeding stopped in 31 patients. Monthly bleeding frequency significant reduced ($p < 0.001$)

ABR, annualized bleeding rate; FVIII, factor VIII; GI, gastrointestinal; IQR, interquartile range; NI, not indicated; VWD, von Willebrand disease. *VWF:RCo IU/kg.

Evidencia científica muestra una disminución de las tasas de hospitalización

2018

Accepted: 14 February 2018

DOI: 10.1111/hae.13473

ORIGINAL ARTICLE

Von Willebrand disease

WILEY Haemophilia

Bleeding-related hospitalization in patients with von Willebrand disease and the impact of prophylaxis: Results from national registers in Sweden compared with normal controls and participants in the von Willebrand Disease Prophylaxis Network

E. Holm[1] | K. Steen Carlsson[2,3] | S. Lövdahl[1] | A. E. Lail[4] | T. C. Abshire[5] | E. Berntorp[1]

Von Willebrand disease

Bleeding-related hospitalization in patients with von Willebrand disease and the impact of prophylaxis: Results from national registers in Sweden compared with normal controls and participants in the von Willebrand Disease Prophylaxis Network

E. Holm[1] | K. Steen Carlsson[2,3] | S. Lövdahl[1] | A. E. Lail[4] | T. C. Abshire[5] | E. Berntorp[1]

Gastrointestinal haemorrhages were dominated as the cause of admissions both before the start of prophylaxis (49%) and after (53%). This type of bleeding remained the most common reason for hospitalization after initiating prophylaxis. Epistaxis was the cause of 21 admissions prior to and 10 admissions following the start of prophylaxis. Two intracranial haemorrhages occurred in two subjects prior to prophylaxis and none during prophylaxis.

3.2 | Data from the VWD PN

One hundred and nine subjects were enrolled in the VWD PN study–96 in a retrospective study and 13 (two of whom withdrew after enrolment) in a prospective study. Of these, 105 subjects were included in the current analysis, ten subjects from the prospective and ninety-five from the retrospective study.

The most common type of VWD was type 3 (52%) followed by type 2A (22%), type 1 (12%), type 2B (9%) and other types (4%). The

Journal of Thrombosis and Haemostasis, **13**: 1585–1589 DOI: 10.1111/jth.12995

IN FOCUS

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

Ajuste de dosis a intensidad y tipo de sangrado

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.

50 UI/kg/día

50 UI/kg/dos veces semana

50 UI/kg/d/tres veces semana

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.

Disminución o prevención de los eventos de sangrado

Joint Bleed
2 or more spontaneous bleeds in the same joint
3 or more in different joints within the last 6 months

Epistaxis
3 or more bleeding episodes requiring VWF or transfusion within the last 6 months

Gastro-intestinal bleeding
2 or more severe GIB requiring VWF or transfusion or with drop in hemoglobin

Menorrhagia
PBAC>185 or requirement of VWF /transfusion within the past year

Cuando

Holm, Blood Coagul Fibrinolysis 2015

Retrospective chart review of GI bleeding in people with von Willebrand disease

Jonathan C. Roberts[1,2] | Miguel A. Escobar[3] | Suchitra Acharya[4] | Nina X. Hwang[5] | Michael Wang[6] | Sarah Hale[7] | Sarah Brighton[8] | Peter A. Kouides[9]

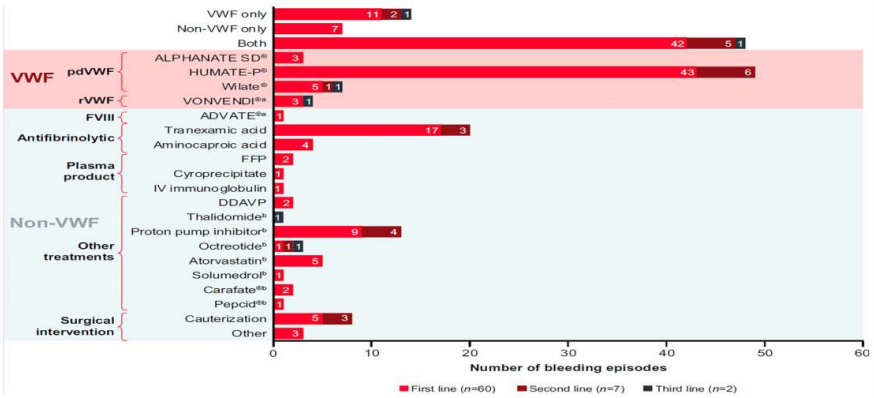
2024

Gastro-intestin bleeding

Haemophilia. 2024;30:970-980.

- Causa más frecuente de hospitalización en VW con importante consumo de recursos: días de estancia, procedimientos realizados, consumo de factor

- Altas tasas de recurrencia, complejidad de manejo con uso de opciones terapéuticas fuera de indicación: fármacos antiangiogénicos



Retrospective chart review of GI bleeding in people with von Willebrand disease

- Papel Factor de Von willebrand como antiangiogénico : déficit de multímeros de alto peso molecular se asocia al desarrollo de malformaciones arteriovenosas

- Los casos con malformaciones arteriovenosas subyacentes : presentan mayores tasas de recurrencia , requieren dosis de factor más altas y la duración de tratamiento hasta cese de sangrado es más largo

- Mayor incidencia y mayor severidad de sangrados en tipo 2A y tipo 3

Indicaciones de profilaxis

- ❑ Al menos dos episodios en los últimos 12 meses
- ❑ Historia de Sangrados severos digestivos

- ❑ Requerimiento de mayores dosis y frecuencia de administración
- ❑ Posible coadyuvancia con otros tratamientos
- ❑ Disminución de frecuencia e intensidad de sangrado
- ❑ Papel de factor de VW recombinante rico en MULTÍMEROS DE MUY ALTO PESO MOLECULAR

2023

EXPERT REVIEW OF HEMATOLOGY
2023, VOL. 16, NO. 6, 435–450
https://doi.org/10.1080/17474086.2023.2166925

Taylor & Francis
Taylor & Francis Group

REVIEW

Check for updates

The diagnosis, natural history, and management of von Willebrand disease in women in the age of guidelines

Sanjana Kalvehalli Kashinath [a] and Peter A. Kouides [a,b]

[a]Department of Hematology Oncology, Mary M. Gooley Hemophilia Center, Inc., The Rochester General Hospital, 14621, Rochester, NY, USA; [b]Department of Hematology Oncology, University of Rochester School of Medicine, Rochester, NY, USA

ABSTRACT

Introduction: Women and girls with bleeding disorders face multiple bleeding challenges throughout their life. The most significant morbidity and mortality are due to heavy menstrual bleeding and postpartum hemorrhage in their reproductive years. The ASH/ISTH/NHF/WFH 2021 guidelines on diagnosing and managing von Willebrand disease (VWD) provide several new updates.

Areas covered: Women with VWD have a higher prevalence of heavy menstrual bleeding. The subpopulation of adolescents is particularly vulnerable, as the diagnosis is often delayed with increased comorbidity of iron deficiency anemia and associated symptoms. A detailed review is done on the prevalence of bleeding-related complications, especially heavy menstrual bleeding (HMB) and postpartum hemorrhage (PPH). The management strategies are also reviewed in detail, with a specific focus on the target factor levels and the use of antifibrinolytics.

Expert opinion: The 2021 ASH/ISTH/NHF/WFH diagnostic and management recommendations are reviewed with a specific focus on hormonal methods of HMB management and antifibrinolytics in this situation. The reviewed topics include neuraxial anesthesia, factor cutoff, and tranexamic acid use in the postpartum period.

ARTICLE HISTORY
Received 21 August 2022
Accepted 6 January 2023

KEYWORDS
Von Willebrand disease; heavy menstrual bleed; postpartum hemorrhage; tranexamic acid; neuraxial anesthesia; guidelines

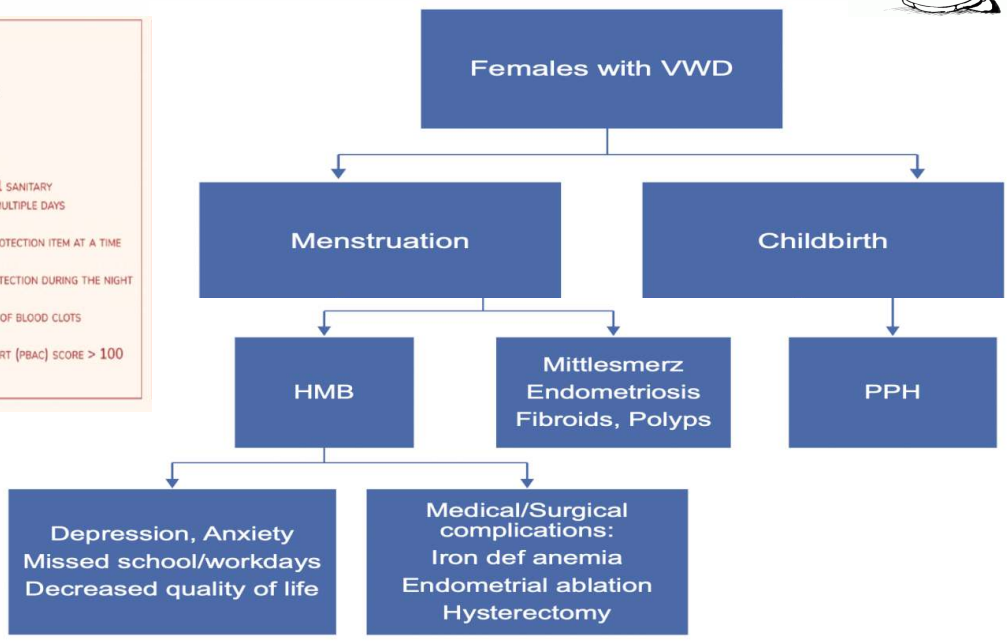
Menorrhagia

The diagnosis, natural history, and management of von Willebrand disease in women in the age of guidelines

VWD

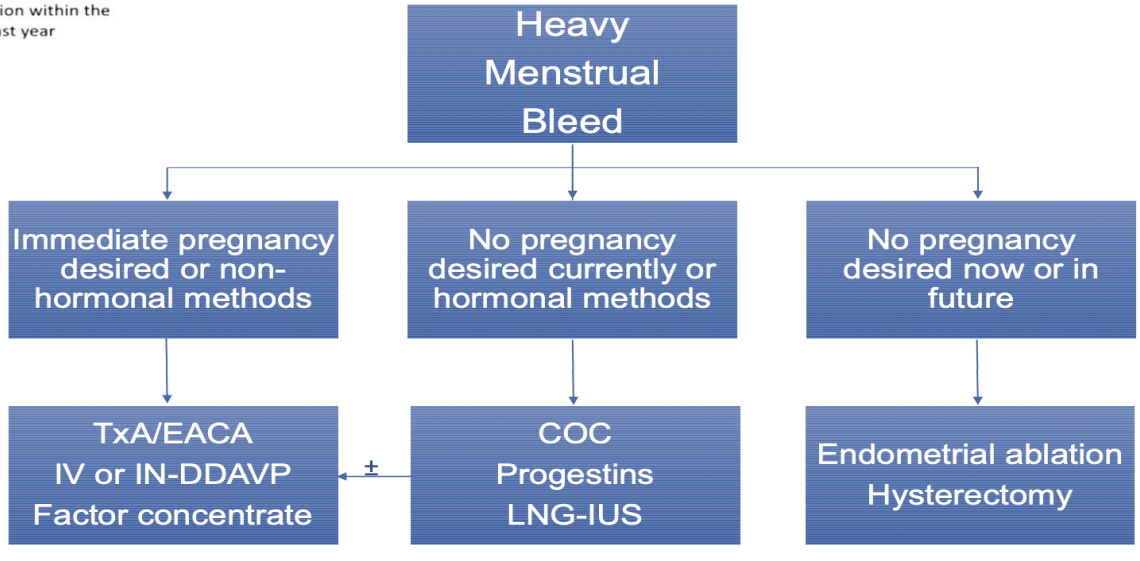
Menstrual bleeding meeting any of the following criteria

- lasting ≥ 8 days
- consistently soaks through ≥ 1 sanitary protections every 2 hours on multiple days
- requires use of > 1 sanitary protection item at a time
- requires changing sanitary protection during the night
- associated with repeat passing of blood clots
- pictorial blood assessment chart (PBAC) score > 100



Menorrhagia
PBAC>185 or requirement of VWF /transfusion within the past year

The diagnosis, natural history, and management of von Willebrand disease in women in the age of guidelines



EACA – Epsilon aminocaproic acid

Joint Bleed
2 or more spontaneous bleeds in the same joint
3 or more in different joints within the last 6 months

Multicenter Study > Haemophilia. 2015 May;21(3):e185-e192. doi: 10.1111/hae.12670. Epub 2015 Apr 9.

Joint bleeds in von Willebrand disease patients have significant impact on quality of life and joint integrity: a cross-sectional study

K P M van Galen [1], Y V Sanders [2], U Vojinovic [2], J Eikenboom [3], M H Cnossen [4], R E G Schutgens [1], J G van der Bom [5 6], K Fijnvandraat [7], B A P Laros-Van Gorkom [8], K Meijer [9], F W G Leebeek [2], E P Mauser-Bunschoten [1]; WiN Study Group

2015

Artropatía estará presente en más del 40% de los pacientes tras episodios de hemartros

Limitaciones funcionales, dolor crónico, deterioro calidad de vida

50% de los pacientes con tipo 3
Al menos el 10 % de pacientes tipo 1 y 2

Casos moderados y severos

63% pacientes con hemartros antes de los 16 años

Comparative Study > Thromb Haemost. 2018 Oct;118(10):1690-1700. doi: 10.1055/s-0038-1670704. Epub 2018 Oct 1.

Long-Term Outcome after Joint Bleeds in Von Willebrand Disease Compared to Haemophilia A: A Post Hoc Analysis

Karin P M van Galen [1], Merel Timmer [1], Piet de Kleijn [1 2], Frank W G Leebeek [3], Wouter Foppen [4], Roger E G Schutgens [1], Jeroen Eikenboom [5], Karina Meijer [6], Karin Fijnvandraat [7], Britta A P Laros-van Gorkom [8], Jos W Twisk [9], Eveline P Mauser-Bunschoten [1], Kathelijn Fischer [10]; WiN Studygroup

2018

Abstract

Long-term outcome after joint bleeds in von Willebrand disease (VWD) (von Willebrand factor activity ≤ 30 IU/dL) could differ from moderate or severe haemophilia A (HA) (factor VIII [FVIII] 1-5 IU/dL or FVIII < 1 IU/dL). We performed a post hoc analysis on Haemophilia Joint Health Score (HJHS, 0-124), X-ray Pettersson scores (PS, 0-13/joint) and the Haemophilia Activities List (HAL, 0-100), using multivariable regression to adjust for age (rate ratio [RR] or odds ratio [OR] [95% confidence interval]). We included 48 VWD (median age, 47 years, type 3 VWD, *n* = 19), 39 moderate HA (median, 39 years) and 59 severe HA patients (median, 25 years) with documented joint bleeds. VWD patients suffered repeated bleeding (lifetime > 5/joint) less often than moderate and severe HA patients (52% vs. 77% vs. 98%). HJHS and PS in VWD were similar to moderate HA (median HJHS 5 vs. 6, RR 0.9 [0.5-1.4] and PS > 3 of ≥ 1 joint OR 0.3 [0.1-1.4]), but better than in severe HA patients (median HJHS 5 vs. 9, RR 1.8 [1.1-2.9]; PS > 3 in any joint OR 0.1 [0.0-0.3]). Self-reported limitations in activities were comparable across VWD, moderate HA (HAL score < 95: 67% vs. 49%; OR 1.4 [0.5-3.6]) and young adults with severe HA (67% vs. 48%; OR 1.7 [0.7-4.4]). Despite fewer joint bleeds, joint outcome after joint bleeds was similar in VWD and moderate HA patients. Type 3 VWD patients had worst joint outcome, comparable to younger intensively treated severe HA patients. Limitations in activities occurred as often in VWD as in both moderate and severe HA.

Qué opciones terapéuticas tenemos

OPCIONES TERAPÉUTICAS

Table 2 Pd-VWF/FVIII Concentrates Licensed in Europe

Product	Brand	Purification	Viral Inactivation	VWF:RCo/Ag (Ratio)	VWF:RCo/FVIII (Ratio)
Alphanate	Grifols	Heparin ligand chromatography	S/D + dry heat (80°, 72h)	0.47 ± 0.1	0.91 ± 0.2
Fanhdi	Grifols	Heparin ligand chromatography	S/D + dry heat (80°, 72h)	0.47 ± 0.1	1.04 ± 0.1
Haemate P	CSL Behring	Multiple precipitation	Pasteurization (60°, 10h)	0.59 ± 0.1	2.45 ± 0.3
Immunate	Baxter	Ion exchange chromatography	S/D + vapor heat (60°, 10h)	0.47	1.1
Wilate	Octapharma	Ion exchange + size exclusion chromatography	S/D + dry heat (100°, 2h)	–	0.9
Wilfactin	LFB	Ion exchange + affinity	S/D, 35 nm filtration, dry heat (80°, 72h)	0.95	50
Veyvondi/ VonVendi	Shire/ Takeda	Chinese Hamster Ovary (CHO) cell line co-expressing the VWF and FVIII genes, in absence of any animal or other human plasma proteins; purified by immune-affinity chromatography	None	1.16 ± 0.25	>100

Abbreviations: VWF, von Willebrand factor; RCo, ristocetin co-factor; Ag, antigen; FVIII, factor VIII; S/D, solvent/detergent.

Data derived from the Online Registry of Clotting Factor Concentrates of the World Federation of Hemophilia (WFH). Available at: https://wfh.org/article/wfh-online-registry-of-clotting-factor-concentrates/

OPCIONES TERAPÉUTICAS

	VWF:RCo/FVIII (Ratio)
Fandhi	1.04 ± 0.1
Haemate P	2.45 ± 0.3
Wilate	0.9
Veyvondi	

Diferentes proporciones de factor VIII y WF:RCo

Comercializado en España

Sólo factor VW

No comercializado en España

Effectiveness of long-term prophylaxis using pdFVIII/VWF concentrate in patients with inherited von Willebrand disease

2022

Lucia Rugeri[1] | Annie Harroche[2] | Yohan Repessé[3] | Dominique Desprez[4] | Brigitte Pan Petesch[5] | Pierre Chamouni[3] | Christine Biron[6] | Birgit Frotscher[7] | Hasan Catovic[8] | Diane Bracquart[8] | Cédric Martin[8] | Marc Trossaërt[9] | Sandrine Meunier[1] | Roseline d'Oiron[10]

Eur J Haematol. 2022;109:109-117.

Abstract

Background: Patients with symptomatic von Willebrand disease (VWD) should be offered long-term prophylaxis (LTP) to prevent recurrent bleedings. Our objective was to evaluate the effectiveness and safety of Voncento®, a plasma-derived FVIII/VWF concentrate (ratio 1:2.4), administrated in LTP.

Methods: We included patients from the OPALE study (May 2016 to April 2021), a French multicenter observational study following patients with inherited VWD, who received a Voncento® LTP during the study period.

Results: Among the 130 OPALE-study patients, 23 patients (12 women) received a LTP and were therefore included. The median (range) age was 16 (1–85) years; 16 patients were type 3, 1 was type 2A, 6 were type 2B. Before inclusion, 19 (83%) were under LTP and 4 (17%) received on-demand (OD) treatment. The indications for initiating prophylaxis in the overall population were joint bleeding (43%), ear, nose, and throat (ENT) bleeding including epistaxis or oral bleeding (39%), and recurrent muscle hematoma (22%). The medians (ranges) dose of Voncento® per infusion, frequency, and weekly dose were 45 (33–109) IU/kg, 2 infusions per week, and 96 (44–222) IU/kg/week, respectively. The median (range) annualized bleeding rate (ABR) was 0.8, 0.7 (0–3.5), and 0 (0–2.3) for type 2A, 2B, 3 patients, respectively. There was no difference regarding to the dose, frequency of infusion, or in terms of ABR in 9/19 patients who replaced previous concentrates with Voncento®. During the study period, no adverse event was reported.

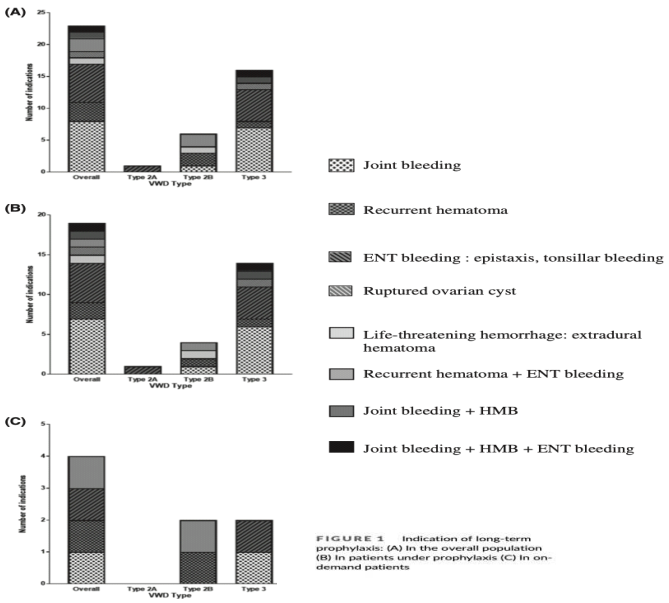


FIGURE 1 Indication of long-term prophylaxis: (A) In the overall population (B) In patients under prophylaxis (C) In on-demand patients

- Disminuye tasa global y frecuencia de sangrados

- No incluye como indicaciones clínicas para inicio de profilaxis: sangrado GI o menstruaciones copiosas como indicaciones aisladas

Eur J Haematol. 2022;109:109-117.

- Subtipos 2B ,2A, 3

TABLE 3 Dose, frequency, duration of follow-up, and bleeding episodes in all patients receiving LTP with Voncento®

	Total n = 23	Type 2A n = 1	Type 2B n = 6	Type 3 n = 16
Dose, IU/kg	45 (33-109)	109	54.5 (33-100)	44 (35-62)
Weekly dose, IU/kg/week	96 (44-222)	109	100.5 (67-200)	90 (44-222)
Number of infusions per week	2 (1-3)	1	2 (1-3)	2 (1-3)
Duration of follow-up, months[a]	19 (5-48)	48	21 (17-27)	17.5 (5-46)
ABR	0.5 (0-7.2)	0.8	0.7 (0-2.9)	0 (0-7.2)
Effectiveness (Excellent/Good)[b]	9/10	0/1	3/3	6/6

Note: Results are expressed as median (range).
Abbreviations: ABR, annualized bleeding rate; LTP, long-term prophylaxis.
[a]One patient remained only for 5 months under LTP.
[b]Effectiveness was not available for 4 patients.

The overall median dose and number of infusions reported herein were similar to those reported in smallest studies and did not differ according to the type of VWD, even if the type of bleeding differed.[12,14] Thus, no significant difference in terms of dose was observed between type 2B and type 3 patients.

Eur J Haematol. 2022;109:109–117.

2024

REGULAR ARTICLE

blood advances

von Willebrand factor/factor VIII concentrate (Wilate) prophylaxis in children and adults with von Willebrand disease

Robert F. Sidonio Jr,[1] Ana Boban,[2] Leonid Dubey,[3] Adlette Inati,[4,18] Csongor Kiss,[5] Zoltan Boda,[6] Toshko Lissitchkov,[7] Laszlo Nemes,[8] Dzmitry Novik,[9] Elina Peteva,[10] Ali T. Taher,[11] Margarita Arkadevna Timofeeva,[12] Kateryna V. Vilchevska,[13] Vladimir Vdovin,[14] Sylvia Werner,[15] Sigurd Knaub,[16] and Claudia Djambas Khayat[17]

Patient eligibility

Patients were eligible if they were diagnosed with VWD type 1 (baseline VWF:RCo <30 IU/dL), 2A, 2B, 2M, or 3, were 6 years and older at the time of screening, and had completed WIL-29. Patients who experienced at least 6 BEs during WIL-29 (excluding menstrual bleeds) of which at least 2 were treated with a VWF-containing product, were eligible for WIL-31. Female patients of child-bearing potential must have had a negative urine pregnancy test at screening and agreed to use adequate birth control measures. In case hormonal contraception was used, the medication class should remain unchanged for the duration of the study.

- Periodo de seguimiento de un año en pacientes previamente a demanda con cualquier factor rico en VW

Study design

WIL-31 (NCT04052698; WILPROPHY) was a prospective, noncontrolled, international, multicenter phase 3 study investigating the efficacy and safety of Wilate prophylaxis in patients with VWD. WIL-31 was preceded by a 6-month prospective run-in study, WIL-29 (NCT04053699), during which patients received on-demand treatment with any available VWF concentrate. During WIL-31, patients received Wilate prophylaxis for 12 months. The recommended dosing of Wilate was 2 to 3 times per week at an intravenous dose of 20 to 40 IU/kg body weight and could be adapted based on individual patient responses. In the case of unacceptably frequent spontaneous breakthrough bleeding events (BEs; ie, >2 spontaneous BEs or 1 major spontaneous BE within a 30-day period), the dose of Wilate was to be increased by ~5 IU/kg. If patients still experienced >2 spontaneous BEs after dose increase, the dosing frequency was increased from 2 times per week to 3 times per week. The decision whether treatment was required to treat breakthrough BEs, and the dose and duration of

- Dosis inicial 20-40 UI/kg 2-3 veces semana

Esquema

- Si sangrado se subirá inicialmente de dosis y si persiste clínica se reajustará frecuencia

End points

The primary end point of WIL-31 was to show a >50% reduction in mean total annualized bleeding rate (total ABR; TABR) during Wilate prophylaxis compared with prior on-demand treatment (ie, during WIL-29). Additional end points included spontaneous ABR (SABR), Pictorial Blood Loss Assessment Chart (PBAC) score for menstrual bleeds, annual rate of heavy menstrual bleeds, Wilate consumption for prophylaxis, incremental in vivo recovery (IVR), treatment-emergent adverse events (TEAEs), and proportion of successfully treated breakthrough bleeds and surgical prophylaxis. The efficacy assessment of treatment of BEs and surgical prophylaxis included the categories "excellent," "good," "moderate," and "none" (supplemental Table 1). All efficacy ratings assessed as either "excellent" or "good" were considered successfully treated.

- Reducción > 50% tasa de sangrado anual

Recombinant von Willebrand factor prophylaxis in patients with severe von Willebrand disease: phase 3 study results

2022

Frank W. G. Leebeek,[1] Flora Peyvandi,[2,3] Miguel Escobar,[4] Andreas Tiede,[5] Giancarlo Castaman,[6] Michael Wang,[7] Tung Wynn,[8] Jovanna Baptista,[9] Yi Wang,[10] Jingmei Zhang,[10] Björn Mellgård,[10] and Gülden Özen[10]

KEY POINTS

- rVWF prophylaxis reduced spontaneous bleeding rates in patients previously on VWF on-demand therapy.
- Patients switching from prophylaxis with plasma-derived VWF to rVWF experienced a similar level of control over their spontaneous bleeding.

International guidelines conditionally recommend long-term prophylaxis in patients with von Willebrand disease (VWD) and severe and frequent bleeding. As recombinant von Willebrand factor (rVWF; vonicog alfa) may reduce the frequency of treated spontaneous bleeding events (BEs), we investigated the efficacy and safety of rVWF prophylaxis in adults with severe VWD. Patients with BEs requiring VWF therapy in the past year (on-demand VWF therapy [prior on-demand group] or plasma-derived VWF prophylaxis [pdVWF; switch group]) were enrolled in a prospective, open-label, nonrandomized, phase 3 study. The planned duration of rVWF prophylaxis was 12 months; starting rVWF dose was 50 ± 10 VWF: ristocetin cofactor (VWF:RCo) IU/kg twice weekly (prior on-demand group) or based on prior pdVWF weekly dose/dosing frequency (switch group). The primary endpoint was annualized bleeding rate (ABR) of treated spontaneous BEs (sABR) during rVWF prophylaxis. Over the 12-month study period, treated sABR decreased by 91.5% on-study vs historical sABR in 13 patients in the prior on-demand group, and by 45.0% in 10 patients in the switch group (model-based analysis ratio, 0.085; 95% confidence interval [CI], 0.021-0.346 and 0.550; 95% CI, 0.086-3.523, respectively). No treated spontaneous BEs were recorded in 84.6% (11/13) and 70.0% (7/10) of patients, respectively. The safety profile of rVWF was consistent with the previously established profile, with no new adverse drug reactions identified. Findings suggest that rVWF prophylaxis can reduce treated spontaneous BEs in patients previously receiving on-demand VWF therapy and maintains at least the same level of hemostatic control in patients who switch from prophylaxis with pdVWF to rVWF, with a favorable safety profile. This trial was registered at www.clinicaltrials.gov (#NCT02973087) and www.clinicaltrialsregister.eu (#EudraCT 2016-001478-14).

blood® 14 JULY 2022 | VOLUME 140, NUMBER 2

Prophylaxis with recombinant von Willebrand factor in patients with type 3 von Willebrand disease: Results of a post hoc analysis from a phase 3 trial

Frank W. G. Leebeek[1] | Flora Peyvandi[2,3] | Andreas Tiede[4] | Giancarlo Castaman[5] | Miguel Escobar[6] | Michael Wang[7] | Bulent Zülfikar[8] | Sophie Susen[9,10,11] | Wolfgang Miesbach[12] | Scarlett Wang[13] | Yi Wang[13] | Jingmei Zhang[13] | Gülden Özen[13]

2023

Eur J Haematol. 2023;111:29-40.

Abstract

Objectives: To describe efficacy/safety of recombinant von Willebrand factor (rVWF) prophylaxis in patients with type 3 von Willebrand disease (VWD).

Methods: This post hoc analysis of a phase 3 open-label trial provides a more detailed analysis of adults with type 3 VWD, categorized based on prior treatment at screening: "Prior On-Demand (OD)" (OD VWF; ≥3 documented spontaneous bleeding events [BEs] requiring VWF in previous 12 months) or "Switch" (plasma-derived [pd] VWF prophylaxis for ≥12 months). Annualized bleeding rates (ABRs) were evaluated during 12 months of rVWF prophylaxis versus historical data from medical records.

Results: In the Prior OD group (n = 10), mean spontaneous ABR (sABR) for treated BEs was reduced by 91.6% (ratio, 0.08; 95% CI, 0.02–0.45) versus mean historical sABR. In the Switch group (n = 8), mean sABR for treated BEs was reduced by 47% (ratio, 0.53; 95% CI, 0.08–3.62). One non-serious adverse event (AE) was considered possibly related to rVWF. No treatment-related, fatal, or life-threatening serious AEs were reported, and no patient developed VWF inhibitors.

Conclusions: rVWF prophylaxis reduced sABR in type 3 VWD patients previously treated with OD VWF therapy, and maintained a similar level of hemostatic control in those switching from pdVWF prophylaxis to rVWF prophylaxis.

KEYWORDS

bleeding, prophylaxis, recombinant von Willebrand factor, von Willebrand disease type 3

Novelty statements

What is the new aspect of your work?

This analysis provides data for recombinant von Willebrand factor (rVWF) prophylaxis in patients with type 3 von Willebrand disease (VWD), a rare population with limited data available, and highlights the prevalence of untreated bleeding events.

What is the central finding of your work?

rVWF prophylaxis effectively reduced bleeding rates in patients with type 3 VWD previously treated with on-demand VWF, and maintained a similar level of hemostatic control in those patients with type 3 VWD switching from plasma-derived VWF prophylaxis to rVWF prophylaxis.

What is (or could be) the specific clinical relevance of your work?

rVWF prophylaxis may reduce the incidence of bleeding events in patients with type 3 VWD.

2023

Expert Review of Hematology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierr20

An evaluation of von Willebrand factor (recombinant) therapy for adult patients living with severe type 3 von Willebrand disease

John M. Hancock & Miguel A. Escobar

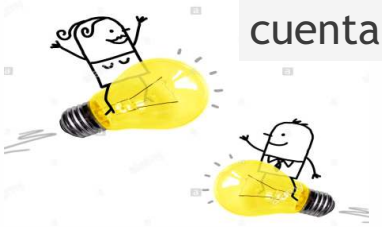
In contrast to patients with severe hemophilia receiving prophylaxis, no data are available on the trough levels that have to be targeted to reduce BEs in patients with type 3 VWD receiving VWF prophylaxis. In this study, we measured trough levels of VWF and FVIII based on clinical visit schedules and not during BEs. As expected, given the half-life of VWF, trough levels of VWF:RCo were below the limit of detection (with the exception of a few outliers) in individuals treated twice weekly. However, FVIII trough levels were in the normal range. This may explain the low rates of severe BEs, especially of joint bleeding, in our cohort. Only one patient (from the Switch group; with trough levels of VWF:RCo below the level of detection and FVIII:C between 1 and 38 IU/dL at assessments between screening and month 9) suffered a spontaneous joint bleed during rVWF prophylaxis. Levels of VWF:RCo and FVIII:C were not available for the specific time period of this joint BE.

- Especialmente eficaz en hemartros

the prior on-demand group, the recommended starting dose regimen was 50 ± 10 VWF:RCo IU/kg twice weekly. In the switch group, the starting dose/dosing frequency was based on the prior pdVWF weekly VWF dose equivalent (within ±10%) divided into 1 to 3 weekly infusions (maximum: 80 VWF:RCo IU/kg per infusion). rVWF dosage could be individualized (maximum: 80 VWF:RCo IU/kg) based on available individual historical PK data, type/severity of historical BEs, and/or monitoring of appropriate clinical and laboratory measures. Study guidelines

- **Tratamientos individualizados : tipo y severidad del sangrado**
- **Apoyo de la farmacocinética**

A tener en cuenta



EXPERT OPINION ON PHARMACOTHERAPY

Expert Opinion on Pharmacotherapy

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ieop20

Factor VIII stimulants and other novel therapies for the treatment of von Willebrand disease: what's new on the horizon?

Katherine Regling & Robert F. Sidonio Jr

2024

OPCIONES TERAPÉUTICAS: estudios cerrados

Drug name (sponsor) [trial name]	NCT (phase)	Eligibility criteria	Treatment	Outcome	Reference
Wilate® (Octapharma) [WILPROPHY]	NCT04052698 (Phase 3)	VWD Types 1 (VWF:RCo <30 IU/dL), 2A, 2B, 2 M, 3 Aged ≥6 years Current on-demand treatment with VWF-containing product with at least 1 (average of ≥ 2) documented spontaneous BEs per month in previous 6 months	Wilate® 20 – 40 IU/kg IV 2–3 times per week for 12 months If frequent bleeding (>2 spontaneous BEs or 1 major spontaneous BE within 30 days), Wilate® was increased by about 5 IU/kg If patients still experienced >2 spontaneous BEs after dose increase, then frequency was increased to 3 times per week Dose and duration of treatment for breakthrough BEs was made by the treating physician	The use of prophylaxis showed a bleed reduction of 84% Efficacy was comparable across VWD type and sites of bleeding Median weekly dose of 58 IU/kg VWF:RCo 70% of patients on twice weekly dosing	[41–43]
Voncento® (CSL Behring) [SWIFT-VWD]	NCT00941616 (Phase 2, 3)	>12 years with VWD (except 2B, N, M) without inhibitors DDAVP ineffective or contraindicated	PK analysis: 80 IU/kg on Days 1 and 180 Prophylaxis: Frequency and dose determined by investigator based on participant condition, previous VWF requirements, response to therapy, weight and reason for use	8/22 patients were transitioned to prophylaxis after the first 12 months of on-demand treatment Non-surgical bleeding events decreased from 304 to 10 with 'excellent' hemostatic efficacy in the 8 patients transitioned	
Voncento® (CSL Behring) [SWIFTLY-VWD]	NCT01213446 (Phase 3)	<12 years with VWD	PK analysis: 80 IU/kg on Day 1 PK analysis at Day 180 for type 3 VWD only	The incidence of major bleeding events was significantly lower in the prophylaxis group (2.2%) compared to the on-demand group (27.1%) Prevention of joint bleeding reduced in prophylaxis group (3.3%) compared to on-demand group (11.5%)	[46]
Voncento® (CSL Behring) [SWIFT-VWDext]	NCT01224808 (Phase 3)	All ages with VWD who required treatment for bleeding events while on prophylaxis	Spontaneous/Trauma-induced Bleeding: 25 – 50 IU/kg VWF:RCo Surgeries: 60 – 80 IU/kg VWF:RCo	Hemostatic efficacy was rated as 'excellent' or 'good' in > 97% in both the on-demand and prophylaxis groups Total of 13 surgeries; 11 surgeries (including 3 major) were rated as 'excellent' and 2 surgeries were rated as 'good' for hemostatic efficacy	[49,50]
Voncento® (CSL Behring)	NCT02552576 (Phase 4)	All ages with VWD type 1/2A (VWF: RCo <20%) and type 3	On demand: usually 40 – 80 iu/kg VWF:RCo (corresponding to 20 – 40 IU/kg FVIII) Prophy adult: 25 – 40 IU/kg VWF: RCo 1-3× week Prophy <12: 40 – 80 IU/kg VWF: RCo 1-3× week	Non-surgical BEs were treated with 1 infusion only in 55.1% (on-demand) and 70.8% (prophylaxis) The median ABR for all non-surgical BEs and for spontaneous BEs improved for both groups when compared to the previous	
Efanesoctocog Alfa (Bioverativ)	NCT04770935 (Phase 1)	18 to 65 years Type 2N or type 3 VWD	Single IV dose with PK sampling in up to the first 10 days after infusion		
BT200 (Medical University of Vienna)	NCT04677803 (Phase 2)	Hemophilia A, Hemophilia A carriers, VWD type 1, VWD 'vincenza type,' and VWD type 2b	SC dosing, days 0, 4, 7 then once weekly Initially dose 3 mg, then week 3 dose of 3-9 mg HA: median dose was 7 mg on day 28 (0.03-0.16 mg/kg). No antibodies seen in HA patients.	Total of 5 patients with type 2B VWD enrolled Significant increase in platelet count, median of 60 to 179 × 10E9/L Circulating VWF:Ag increased from a median of 64% to 143%; FVIII:C increased from a median of 67% to	

Definición esquemas profilaxis

Farmacocinética

Manejo eventos agudos

Farmacocinética

Subtipos etiológicos

OPCIONES TERAPÉUTICAS: estudios activos

[trial name]	NCT (phase)	Eligibility criteria	Treatment	Study status	References
Wilate® (Unity Health Toronto) [EMPOWER]	NCT0620509 (Phase 3)	VWD (any type) Females ≥18 years Modified PBAC > 100 Stable treatment for HMB and IDA for three cycles prior	Treatment Period 1: Randomized to Wilate® or placebo (normal saline) plus standard of care for four cycles Wilate® or Placebo given for the two anticipated heaviest days of bleeding every 24–48 hours, minimum of two doses Followed by one cycle washout period Treatment Period 2: Crossover to comparator treatment		
Wilate® (Octapharma) [WIL-33]	NCT04953884 (Phase 3)	VWD Types 1 (VWF:RCo <20%), 2A, 2B, 2 M, 3 Aged <6 years Minimum BW of 12.5 kg	PK: Single dose Wilate® of 80 IU/kg IV Prophylaxis: Wilate® 30 – 50 IU/kg IV administered 2–3 times per week Minor hemorrhage: Loading dose of Wilate® of 30 – 50 IU/kg IV, followed by maintenance dose of 30 – 40 IU/kg IV every 12-24 hours to achieve VWF:RCo and FVIII:C trough levels of > 30% Major hemorrhage: Loading dose of Wilate® of 50 – 80 IU/kg IV, followed by maintenance dose of 30 – 50 IU/kg IV every 12-24 hours to achieve VWF:RCo and FVIII:C trough levels of > 50% Minor Surgery: Loading dose of Wilate® of 40 – 60 IU/kg IV, followed by maintenance dose of 20 – 30 IU/kg IV every 12-24 hours (up to 3 days) to achieve VWF:RCo peak levels of 50% after loading dose and trough levels of > 30% during maintenance Major Surgery: Loading dose of Wilate® of 60 – 80 IU/kg IV, followed by maintenance dose of 30 – 40 IU/kg IV every 12-24 hours (up to 6 days or longer) to achieve VWF:RCo peak levels of 100% after loading dose and trough levels of > 50% during maintenance	Active, not recruiting	[70]
Fanhdi® (Grifols Therapeutics, LLC)	NCT02472665 (Phase 4)	Severe VWD Types 2, 3 (VWF:RCo <15-20 IU/dl) or VWF: Act <15-20 IU/dL Aged <6 years	PK: Single dose Fanhdi® of 80 IU/kg VWF:RCo IV VWD Type 3 subjects will have 2nd PK evaluation 6 months after the first infusion with a reduced sampling schedule	Recruiting	[71]
Vonvendi® ± Advate® (Takeda)	NCT02932618 (Phase 3)	VWD Types 1 (VWF:RCo <20 IU/dL), 2A (VWF:RCo <20 IU/dL), 2B (by genotype), 2N (FVIII:C < 10% and genotype), 2 M, 3 (VWF:Ag ≤ 3 IU/dL) Aged 0 to <18 years	Participants will receive Vonvendi® with or without Advate® for non-surgical BEs, elective surgery, and emergency surgery over the period of 12 to 18 months Elective Surgery: Infuse 12-24 hours prior and within 3 hours of surgery Minor: Infuse every 12–24 hours for at least 48 hours Oral Infuse at least once within first 8-12-hour post-surgery Major: Infuse every 12–24 hours for at least 96 hours Emergency Surgery: Infuse within 3 hours prior to surgery Minor: Infuse every 12–24 hours for at least 48 hours Oral: Infuse at least once within first 8-12-hour post-surgery Major: Infuse every 12–24 hours for at least 96 hours	Recruiting	[73]
Alphan (Grif	ICT00555555 (Phase 4)	≥7 years VWD Type 3 Surgical intervention required (At least 10 surgeries to be considered as major)	Dosing: Maximum 80 IU/kg VWF:RCo Frequency: Dependent upon clinical condition and type of surgery	Active, not recruiting	[74]
Emicizumab (Bleeding and Clotting Disorders Institute and Genentech, Inc.)	NCT05500807 (Phase 1)	Severe Type 3 VWD, VWF:Ag/VWF:RCo/VWF Collagen binding ≤ 20% Variant VWD confirmed by genetic testing with VWF: Ag/VWF:RCo/VWF collagen binding < 50% Hemophilia A + VWD with VWF:Ag/VWF:RCo/VWF collagen binding < 50%	3 mg/kg weekly x4 weeks (loading dose) 1.5 mg/kg once weekly x1 year (prophylaxis) *Dose up-titration to 3 mg/kg once weekly will be allowed after 24 weeks on emicizuma prophylaxis in the case of suboptimal efficacy*		

Abbreviations: BW, body weight; FVIII:C, factor VIII activity; HMB, heavy menstrual bleeding; IV, intravenous; IDA, iron deficiency anemia; PBAC, pictorial blood assessment chart; PK, pharmacokinetic; VWD, von Willebrand disease; VWF:Act, von Willebrand factor activity; VWF:Ag, von Willebrand factor antigen; VWF:RCo, von Willebrand factor ristocetin cofactor activity.

Metrorragias

Manejo eventos agudos

Subtipos etiológicos

Menorrhagia
PBAC>185 or requirement of V\ /transfusion within past year

Drug name (sponsor) [trial name]	NCT (phase)	Eligibility criteria
Wilate® (Unity Health Toronto) [EMPOWER]	NCT06205095 (Phase 3)	VWD (any type) Females ≥18 years Modified PBAC > 100 Stable treatment for HMB and IDA for three cycles prior

EXPERT OPINION ON PHARMACOTHERAPY 2024, VOL. 25, NO. 11, 1427–1438
https://doi.org/10.1080/14656566.2024.2391526

>100 will be eligible to participate. Participants will be randomized to receive either Wilate®, a plasma-derived (pd) VWF: FVIII factor or normal saline infusions along with the standard of care for heavy menstrual bleeding for four cycles. Wilate® will be given as prophylaxis for the two anticipated heaviest days of bleeding every 24–48 h for a minimum of two doses. The four cycles will be followed by one washout cycle, and then there will be crossover to the comparator treatment during the second treatment period. The primary and secondary outcomes will assess the effect of prophylaxis on clinical outcomes of 2–3 doses of pdVWF:FVIII when given during the first 4 days of menstruation compared to placebo as well as interindividual changes in menstruation, standard of care therapies and laboratory parameters, respectively.

EXPERT OPINION ON PHARMACOTHERAPY
2024, VOL. 25, NO. 11, 1427–1438
https://doi.org/10.1080/14656566.2024.2391526

of care for heavy menstrual bleeding for four cycles. Wilate® will be given as prophylaxis for the two anticipated heaviest days of bleeding every 24–48 h for a minimum of two doses. The four cycles will be followed by one washout cycle, and then there will be crossover to the comparator treatment during the second treatment period. The primary and secondary outcomes will assess the effect of prophylaxis on clinical outcomes of 2–3 doses of pdVWF:FVIII when given during the first 4 days of menstruation compared to placebo as well as interindividual changes in menstruation, standard of care therapies and laboratory parameters, respectively.

Esquema

Emicizumab

EXPERT OPINION ON PHARMACOTHERAPY
2024, VOL. 25, NO. 11, 1427–1438
https://doi.org/10.1080/14656566.2024.2391526

factor X, facilitating the action of factor X. With its overwhelming success in the treatment of patients with hemophilia A, it was hypothesized that it may benefit individuals with severe VWD, since they have FVIII levels in the hemophilia moderate-to-severe deficiency range. There have been few reports of successful off-label use over the last 5 years, including patients with severe VWD with and without inhibitors [24,78–82]. All reported patients have shown excellent response to treatment with minimal breakthrough bleeding. Barg et al. demonstrated that ex vivo spiking with emicizumab increased thrombin generation in plasma from patients with type 3 VWD. A total of 24 patients were included and showed that ETP levels reached the levels of normal controls when spiked with either Haemate P or emicizumab. Although, peak height also improved with both Haemate P and emicizumab, spiking with emicizumab improved the peak height of thrombin generation to a lesser extent. In addition, the group successfully treated a patient with severe VWD with 51 weeks of monitoring prior

Emicizumab

pared to the FVIII concentrate [83]. Most recently, there is an open label clinical trial to establish the efficacy and safety of emicizumab for the treatment of prophylaxis in severe VWD and VWD/hemophilia A [Investigator initiated study by Bleeding and Clotting Disorders Institute, NCT05500807] [84]. Patients ≥ 2–90 years of age with severe type 3 VWD, VWF:Ag/VWF:RCo/VWF collagen binding ≤20%, variant VWD confirmed by genetic testing with VWF:Ag/VWF:RCo/VWF collagen binding <50%, and hemophilia A in combination with VWD with VWF:Ag/VWF:RCo/VWF collagen binding <50% will be included. Efficacy will be assessed by using the ABR in the previous 12 months prior to enrollment and for 18 months after enrollment. The estimated enrollment is 40 patients, and the clinical trial is actively recruiting.

EXPERT OPINION ON PHARMACOTHERAPY
2024, VOL. 25, NO. 11, 1427–1438
https://doi.org/10.1080/14656566.2024.2391526

- Tratamientos adaptados al subtipo de sangrado
- Tratamientos adaptados a la intensidad del sangrado
- Tratamientos adaptados a cada subtipo etiológico

Evidencia clínica definitiva de la superioridad de un régimen profiláctico sobre tratamiento a demanda : estudios clínicos randomizados

- A valorar en epistaxis de repetición , metrorragias, sangrados gastrointestinales, hemartros y hematomas de repetición en función de intensidad y frecuencia de los mismos.

Valoración de impacto en calidad de vida

Evidencia clínica definitiva de la superioridad de un régimen profiláctico sobre tratamiento a demanda : estudios clínicos randomizados

- Se desconoce la mejor pauta en cuanto a dosis y frecuencia de administración.

Frecuencias de administración 2 a 3 veces /semana reajustables en función de la clínica tanto en dosis como en frecuencia

Evidencia clínica definitiva de la superioridad de un régimen profiláctico sobre tratamiento a demanda: puntos de mejora

- Se desconoce la mejor pauta en cuanto a dosis y frecuencia de administración
- Duración . Se debe reevaluar periódicamente
- Impacto real en calidad de vida
- Impacto socioeconómico

Mejorar evidencia científica

Grupos de registro

Ampliar oferta terapéutica

Tratamientos personalizados

Tratamientos personalizados

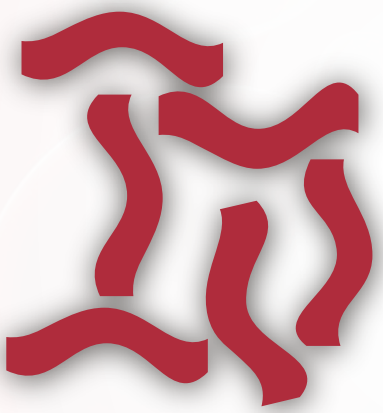
- ❑ Adaptados al subtipo de VW
- ❑ Adaptados al perfil de sangrado: tipo, frecuencia y severidad
- ❑ Adaptados al perfil clínico del paciente: comorbilidades, actividad física
- ❑ Papel futurible de la farmacocinética

Ampliar y mejorar oferta terapéutica

- ❑ Tratamientos adaptados al subtipo de VW
- ❑ Tratamientos con mayor vida media
- ❑ Necesidad de la introducción de la farmacocinética como un instrumento más

BIBLIOGRAFÍA:

1. Guías ISTHASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease. Nathan T. Connell, * Veronica H. Flood, * Romina Brignardello-Petersen, Rezan Abdul-Kadir,4 Alice. Blood advances. 2021. Vol 5, NO 1
2. Translatting the success of prophylaxis in haemophilia to Von Willebrand disease. Wolfang Miesbach. Erik Berntorp Thrombosis Research 199(2021) 67-74
3. Beyond the guidelines: how we approach challenging scenarios in the diagnosis and management of von Willebrand disease. Mouhamed Yazan. Paula D. James. Veronica H. Flood. Nathan T. Connell. JTH. 2023;21: 204-214
4. Prophylactic management of patients with Von Willebrand disease. Massimo Franchini, omid Seidizadeh and Pier Manuccio Manucci. Ther Adv Hematology .2021, vol 12:1-12
5. Retrospective chart review of GI bleeding in people with Von Willebrand disease. Jonathan C. Roberts. Miguel A. Escobar. Suchitra Acharya. Haemophilia 2024, 30:970-980
6. The diagnosis, natural history, and management of Von Willebrand disease in women in the age of guidelines. Sanjana Kalvehall Kasdinath and Peter Kouides. Expert review of Hematology .2023, vol 16. No 6. 435-450
7. Effectiveness of long-term prophylaxis using pdFVIII/VWF concentrate in patients with inherited Von Willebrand disease. Lucia Rugeri. Annie Harroche. Yohan Repesse .Eur J Haematology .2022. 109-117
8. Von Willebrand factor/factor VIII concentrate/Wilate) prophylaxis in children and adults with Von Willebrand disease. Robert F. Sidonio Jr Ana Boban. Blood advances .2024. Volumen 8 number 6
9. Recombinant Von Willebrand factor prophylaxis in patients with severe Von Willebrand disease: phase 3 study results. Frank W.G Leebeck Flora Peyvandi. Miguel Escobar. Andrea Tiede. Blood 2022. Volume 140, number 2
10. An evaluation of Von Willebrand factor (recombinant) therapy for adult patients living with severe type 3 Von Willebrand disease. John M. Hancock. Miguel Escobar. Expert review of hematology. 2023.Vol 16. No 3. 157-161
11. Factor VIII stimulants and other novel therapies for the treatment of Von Willebrand disease: what´s new on the horizon? Katherine Regling. Robert F. Sidonio. Expert opinion on Pharmacotherapy .2024, vol 25, No 11 1427-1438.



REAL
FUNDACIÓN
VICTORIA
EUGENIA

REAL FUNDACIÓN VICTORIA EUGENIA

Seminario Online

“La enfermedad de Von Willebrand: Manejo de las cirugías y profilaxis”

6
noviembre 2024

18:00
horas

MODERADORA:
DRA. MARIANA CANARO HIRNYK

FILIACIÓN: Médico adjunta de la Sección de Hemostasia y Trombosis, Hospital Universitario Son Espases, Palma de Mallorca.

PONENTE:
DRA. ANA MARCO RICO

PONENCIA: "Manejo perioperatorio de la enfermedad de von Willebrand.”
FILIACIÓN: Médico especialista en la Unidad de Hemostasia y Trombosis, Servicio de Hematología. Hospital General Universitario Dr. Balmis, Alicante. Profesora asociada en la Universidad Miguel Hernández.

PONENTE:
DRA. Mª ELSA LÓPEZ ANSOAR

PONENCIA: "Tratamiento profiláctico en enfermedad de Von Willebrand: cuándo y cómo hacerlo. Opciones terapéuticas.”
FILIACIÓN: Servicio de Hematología y Hemoterapia del Complexo Hospitalario Universitario Álvaro Cunqueiro de Vigo.

CON LA COLABORACIÓN DE:

octapharma®

www.rfve.es rfve@rfve.org

REAL
FUNDACIÓN
VICTORIA
EUGENIA