

Reflections on the importance of factor VIII and von Willebrand factor pharmacokinetics in the safety and efficacy of current von Willebrand factor concentrates

Reflexiones sobre la importancia de la farmacocinética de los factores VIII y von Willebrand en la seguridad y la eficacia de los actuales concentrados de factor von Willebrand

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Abstract

Prophylaxis in von Willebrand disease is addressed, focusing on the composition and efficacy of von Willebrand factor concentrates. Three products with different characteristics in terms of their origin and composition (Veyvondi®, Wilate®, and Wilfact®) are compared, highlighting their differences in weekly consumption, infusions and thrombotic events. The results indicate that Wilate® has a lower weekly intake and comparable efficacy in reducing bleeding. The accumulation of factor VIII and its relationship with thrombotic risk are discussed, underlining the importance of precise dosing to maximize efficacy and minimize safety and economic risks.

Keywords: von Willebrand disease. Prophylaxis. FVIII/VWF ratio. Randomized controlled trials. Thrombin generation.

Resumen

Se aborda la profilaxis en la enfermedad de von Willebrand, enfocándose en la composición y la eficacia de los concentrados de factor von Willebrand. Se comparan tres productos con características diferentes en cuanto a su origen y composición (Veyvondi®, Wilate® y Wilfact®), destacando sus diferencias en consumo semanal, infusiones y eventos trombóticos. Los resultados indican que Wilate® tiene un menor consumo semanal y una eficacia comparable en la reducción de sangrados. Se discute la acumulación de factor VIII y su relación con el riesgo trombótico, subrayando la importancia de la dosificación precisa para maximizar la eficacia y minimizar riesgos de seguridad y económicos.

Palabras clave: Enfermedad de von Willebrand. Profilaxis. Ratio FVIII/FVW. Ensayos clínicos controlados. Generación de trombina.

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Introduction

Long-term prophylaxis in the context of von Willebrand disease (VWD) is an area of growing interest regarding its management, especially in patients with a severe or frequent bleeding phenotype. Despite the scarcity of prospective, controlled studies evaluating the efficacy of this therapeutic option, there is significant discrepancy surrounding the composition of von Willebrand factor (VWF) concentrates. These VWF concentrates may or may not contain factor VIII (FVIII), and among the VWF concentrates with FVIII, differences have been reported in the FVIII: VWF ratio. Finally, it is also unclear what the most appropriate FVIII: VWF ratio is in terms of treatment efficacy.

VWF concentrates were originally developed for the treatment of hemophilia A and are used in patients who do not respond to desmopressin or when it is contraindicated. The available concentrates can be of plasma-derived or recombinant origin. The only recombinant VWF concentrate (rVWF), Veyvondi[®],¹ only contains VWF and is obtained from a Chinese hamster ovary cell line. Plasma-derived VWF concentrates can be categorized by their varying purity. Wilate[®]² is a high-purity concentrate, with FVIII in a FVIII: VWF ratio of 1:1, while Wilfact[®]³ is a pure VWF plasma concentrate (FVIII: VWF < 0.2:1). Due to differences in the manufacturing process, design, and factor ratio⁴ (Table 1), it is important to know their precise dosing, given the implications this can have on the safety and efficacy of these concentrates, as well as on the financial impact it may have on the hospital pharmacy.

Method

Based on published scientific evidence, we compared the median annual bleeding episodes (annualized bleeding rate [ABR]), the median weekly consumption (in IU of ristocetin cofactor activity [VWF: RCo]/kg), and the median weekly infusions for long-term prophylactic treatment with the 3 above-mentioned VWF concentrates, as well as their safety surrounding thrombotic events. These 3 concentrates were chosen once data from prospective studies evaluating, among other things, the efficacy of prophylaxis were used for comparison purposes. For Veyvondi[®], post-hoc analysis data from the prospective clinical trial NCT02973087 were considered¹, and for Wilate[®], data from the prospective clinical trial NCT04052698 were taken into consideration². For Wilfact[®], data were taken from a prospective post-marketing observational trial.³

Efficiency analysis of the 3 VWF concentrates was also conducted using generative artificial intelligence (ChatGPT-4[®]).

Results

When evaluating the results, Wilate[®] shows lower weekly consumption vs pure VWF concentrates, Veyvondi[®] and Wilfact[®] (median of 58, 92.6, and 87 IU/kg, respectively). The median weekly infusions for the 3 products are the same (2), without loss of efficacy (ABR 1.9, 2.35, and 1, respectively). Regarding thrombotic events, none have been reported with Wilate[®] throughout its clinical development in more than 200 patients,^{2,5-7} nor with Wilfact[®]. One case of deep vein thrombosis was reported in 1 leg during major hip replacement surgery with Veyvondi[®] (Table 2).⁸

To determine the efficiency of the 3 products, ChatGPT-4[®] considered the reduction in the bleeding rate and the median reported consumption of VWF after analyzing the 3 reports. According to ChatGPT-4[®], Wilate[®] could be considered the most efficient due to its lower weekly consumption and efficacy in reducing bleeding, although Veyvondi[®] also shows excellent efficacy in terms of bleeding reduction.

Discussion

One of the greatest challenges in managing VWD, aside from hemostatic management, is the accumulation and monitoring of FVIII, especially in cases of intensive treatment, such as after a severe trauma or surgery. FVIII levels > 150% are thought to be associated with a higher thrombotic risk.⁹

It would seem logical somehow to think that the use of pure VWF concentrates would be free from this risk. However, thrombotic events have been reported during scheduled surgical procedures in the clinical development of Veyvondi[®],⁵ as well as with other VWF/FVIII concentrates with a lower FVIII proportion than Wilate[®] (e.g., Haemate-P[®] with a VWF: FVIII ratio of 2.4:1, Fanhdi/Alphanate[®]).^{10,11} Thrombotic risk due to FVIII accumulation does not seem to be due to the presence or absence of FVIII in the VWF concentrate, but rather could be due to the different pharmacokinetic behavior of the 2 factors in these products. Free VWF (pure VWF concentrates or those with a lower proportion of FVIII than VWF) causes a delayed elevation of FVIII levels, peaking at 12–24 hours (Fig. 1).¹² In the case of intensive treatment, such as in surgery, especially major surgeries, this phenomenon could cause FVIII

Table 1. Content of VIII, VWF, and the VWF/FVIII ratio in various FVIII concentrates

Product	FVIII (IU/mL)	VWF (IU/mL)	VWF/FVIII
Intermediate purity			
Haemate-P®	28	71	2.5
Profilate SD®	45	145	3.2
Kryobulin TIM3®	33	157	4.8
High purity			
Octavi®	23	14	0.6
Koate HP®	156	144	0.9
Immunate®	85	74	0.9
Beriate®	25	4.3	0.2

FVIII: factor VIII; VWF: von Willebrand factor.

Adapted from Berntorp.⁴**Table 2.** Consumption, efficacy, and infusion frequency of analyzed VWF concentrates

Parameters	Veyvondi® ¹	Wilate® ²	Wilfact® ³
Consumption (IU VWF/kg), median	92.6	58	87
Weekly frequency, median	2	2	2
ABR, median	2.35	1.9	1

VWF: von Willebrand factor; ABR: annualized bleeding rate.

accumulation. With Wilate®¹³ (VWF/FVIII ratio 1:1), all VWF is completely saturated with FVIII, so it cannot bind to the patient's endogenous FVIII. Immediately after infusion, the FVIII peak coincides with the VWF peak, and both factors are eliminated at the same rate,^{5,13} without sustained FVIII accumulation in intensive treatment situations.⁵

In terms of bleeding prophylaxis efficacy, the 3 VWF concentrates achieve acceptable ABRs. Although the median number of weekly infusions is the same for all of them (2), weekly consumption in IU of VWF: RCo differs significantly, being lower for Wilate®.¹⁻³ Why? Firstly, it could be due to the presence of FVIII leading to higher thrombin peaks. In fact, Rugeri et al.¹² reported that a low thrombin peak was associated with a higher risk of bleeding in patients with VWD, and their results suggest that the delay and reduction in thrombin generation in VWD could probably be mainly attributed to a decrease in FVIII plasma concentration in patients with this disorder (Figs. 2 and 3). Berger et al.¹³ reported a reduction in total ABR (from 7.5 down to 2) after switching to Wilate® in a type 3 VWD patient previously

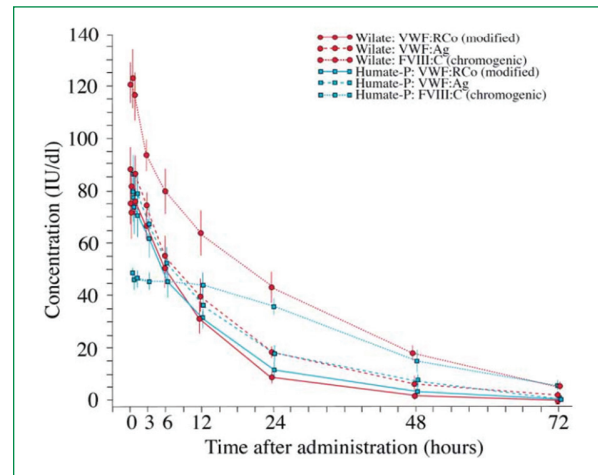


Figure 1. Mean plasma concentrations for VWF and FVIII in subjects with type 3 VWD after the administration of Wilate® and a VWF-rich VWF concentrate (adapted from Kessler et al.).⁵ The observed decay curves for VWF: RCo are similar between Wilate® and HumateP® for subjects with type 3 VWD; the FVIII: C curves are markedly different. For Wilate®, a nearly parallel decrease throughout time is observed for VWF: RCo and FVIII. For Humate-P®, after peaking, the FVIII curve shows a plateau of approximately 12 hours. VWF: von Willebrand factor; FVIII: factor VIII; VWD: von Willebrand disease; RCo: ristocetin cofactor activity; C: coagulant activity.

on Wilfact® prophylaxis 3 times/week (42 IU/kg dose), maintaining a similar prophylaxis regimen.

Secondly, the difference in thrombin peaks generated with Veyvondi® and Wilate® could be due, same as FVIII accumulation, to the interaction and pharmacokinetics of VWF and FVIII. In the case of rVWF, while the infused exogenous VWF is eliminated (half-life of, approximately, 12–15 hours), endogenous FVIII takes longer to normalize and does not peak until 12–24 hours (Fig. 3),^{7,13} when the amount of VWF is lower. With Wilate®, the obtained FVIII peak is higher and reached right after infusion, coinciding with the VWF peak and favoring the formation of a higher thrombin peak.¹³

In fact, this likely impacts the efficacy of the products; Leebeek himself¹ states that “rVWF prophylaxis maintained a similar level of hemostatic control in patients who switched from plasma-derived VWF prophylaxis to rVWF prophylaxis,” not superior.

Finally, in terms of efficiency, the unit cost of the products (Veyvondi® is pending reimbursement price in Spain) nor the fact that in some situations, Veyvondi® may require co-administration of FVIII concentrates within the first 24 hours,² – an aspect that should

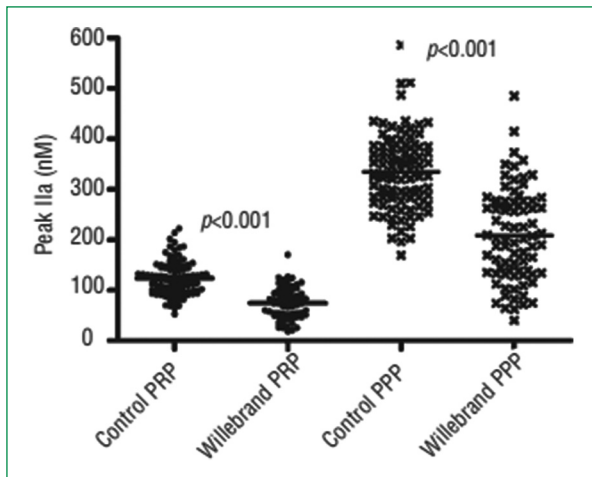


Figure 2. Maximum thrombin generation values in patients with VWD and controls (*adapted from Rugeri et al.*).¹² Peak IIa (thrombin peak): thrombin peak; PPP: platelet-poor plasma; PRP: platelet-rich plasma.

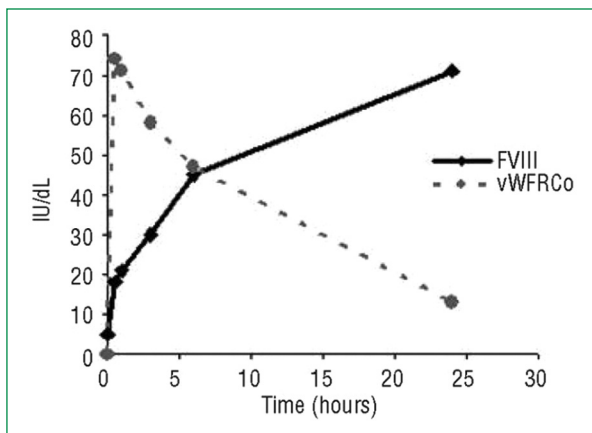


Figure 3. Progression of VWF and FVIII levels after the administration of FVIII-poor VWF concentrates (*adapted from Rugeri et al.*).¹² VWF: RCo: von Willebrand factor ristocetin cofactor activity; VWF: von Willebrand factor; FVIII: factor VIII.

obviously negatively impact the product efficiency – has not been considered in the analysis.

Conclusions

Recognizing the limitations this approach may present, this analysis seems to support the idea that the balance between FVIII and VWF in the content of VWF concentrates may be key in terms of safety, efficacy, and efficiency, the long-term treatment and prophylaxis of VWD, and in the financial implications associated

with treatment. However, more controlled clinical trials with sufficiently large numbers of patients are needed to confirm these observations and help clinicians select the most appropriate VWF concentrate for bleeding treatment and prophylaxis in patients.

Funding

None declared.

Conflicts of interest

None declared.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that they have indeed used generative artificial intelligence, specifically ChatGPT-4, for the efficiency analysis of the 3 treatments, through the analysis of the results reported in the different studies.

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