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Clinical Efficacy and Safety of Fanhdi®, a Plasma-Derived VWF/Factor VIII Concentrate, in von Willebrand Disease in Spain: A Retrospective Study

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Abstract

Objective: To evaluate the efficacy and safety of a plasma-derived factor VIII concentrate containing von Willebrand Factor (pdVWF/FVIII) in standard clinical practice in von Willebrand Disease (VWD) patients.

Methods: A retrospective, multicentric, observational study of VWD patients treated with Fanhdi®, a pdVWF/FVIII concentrate, from January 2011 to December 2017 was conducted at 14 centers in Spain. Efficacy and safety were evaluated for acute bleeding episodes, for prevention of bleeding in surgeries, and for secondary long-term prophylaxis.

Results: Seventy-two eligible patients, type 1, 2, 3 VWD (25%/38.9%/36.1%) were treated for spontaneous and traumatic bleeding (140 episodes, n = 41 patients), to prevent surgical bleeding (69 episodes, n = 43 patients); and for secondary long-term prophylaxis (18 programs, n = 13 patients). Replacement therapy with pdVWF/FVIII showed an excellent to good clinical efficacy in 96.7% of the bleeding episodes, 100% during surgical procedures and 100% during prophylaxis. No adverse events (AEs), nor serious AEs related to the product were observed.

Conclusions: Fanhdi® was effective, safe and well tolerated in the management of bleeding episodes, the prevention of bleeding during surgeries, and for secondary long-term prophylaxis in VWD patients.

Keywords

von willebrand factor, plasma-derived von willebrand factor/factor VIII concentrate, bleeding, surgery, prophylaxis, von willebrand disease

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Introduction

Von Willebrand disease (VWD) is the most common hereditary blood-clotting disorder. It is caused by a deficiency of von Willebrand factor (VWF) and is subdivided into types 1, 2, and 3.[1] Type 1 (70%-80% of cases) is characterized by a quantitative deficiency of VWF. Type 2 (20% of cases) is caused by dysfunctional VWF that results in a normal or reduced VWF antigen concentration and is further subdivided in 2A, 2B, 2M and 2N subtypes. Type 3 VWD (<5% cases) is the most severe form and is due to the absence of circulating VWF and greatly reduced factor VIII (FVIII) levels.[1] VWD prevalence ranges from 0.1 to 1% of the general population.[2,3] In Spain, it is estimated to be 122 patients per million.[4]

The most common clinical symptoms in VWD patients are mild to moderate mucocutaneous bleeding, epistaxis, bruising, menorrhagia, gastrointestinal bleeding, and prolonged bleeding after haemostatic challenges. Joint bleeds occur in approximately half of the patients with type 3 VWD, but also in 5 to 10% of type 1 and type 2 patients. Recurrent joint bleeds can result in arthropathy in VWD patients with FVIII levels <10 IU/dL.[1,5,6]

VWD treatment is aimed primarily at increasing endogenous VWF levels using vasopressin analogues, such as desmopressin (DDAVP), or replacement therapy using FVIII/VWF concentrates.[7] DDAVP is effective in some patients with type 1 VWD and for some patients with type 2 VWD, whereas FVIII/VWF concentrates are the first choice when DDAVP is ineffective or contraindicated (as in severe type 1, type 2 and type 3 VWD).[8,9] Several FVIII/VWF concentrates are commercially available with published efficacy and pharmacokinetic (PK) data.[10–12] According to the treatment strategy for VWD, it is preferred to know the VWF:RCo/FVIII:C ratio to reduce thrombotic risk due to secondary FVIII elevation after repeated administration.[13]

In severe forms of VWD, patients may experience hemarthrosis episodes and severe gastrointestinal bleeding requiring long-term prophylactic treatment with plasma-derived FVIII concentrates containing VWF (pdVWF/FVIII). The VWD Prophylaxis Network international study group showed a significant reduction in the annualized bleeding rate (ABR) for epistaxis, gastrointestinal and joint bleeds after long-term secondary prophylaxis with FVIII/VWF concentrates.[14]

Fanhdi® (Grifols, Barcelona, Spain) is a pdVWF/FVIII concentrate indicated for treatment and prophylaxis of bleeding in haemophilia A patients, and for treatment of bleeding and prophylaxis of surgical bleeding in VWD patients, when desmopressin is ineffective or contraindicated.[11,15–18] PK, efficacy and safety parameters have been evaluated in a prospective, multicentre study to prevent bleeding episodes and during surgical procedures in VWD patients.[11] In addition, two retrospective studies showed excellent or good responses with Fanhdi® in bleeding episodes (92%-95%), and in surgical procedures (93%-98%), without reporting adverse reactions (AR)[15,17] .

Although the efficacy and safety of Fanhdi® in VWD has been proven in clinical trials,[11,17] studies on its efficacy and safety in standard clinical practice are limited. Real-world data covering a broader and more representative patient population could improve patient management and optimize healthcare resources. The study aimed to retrospectively evaluate the clinical efficacy and safety of Fanhdi® in routine clinical practice in VWD patients.

Materials and Methods

Study Design

This was a retrospective, multicentre, observational study of patients diagnosed with VWD that were treated with a pdVWF/FVIII concentrate (Fanhdi®) for acute bleeding episodes, prevention of bleeding during surgery and for prophylaxis of bleeding complications. The study was a retrospective analysis of clinical data obtained under standard clinical practice conditions. The study was conducted in full conformity with appropriate local laws and regulations and the Declaration of Helsinki. The original protocol was approved by the Institutional Review board/Ethics Committee.

Study Drug

Fanhdi® is a highly purified pdVWF/FVIII concentrate. Due to its multimeric structure, the VWF contained is functionally active to promote platelet adhesion to subendothelial structures.[19] The manufacturing process includes heparin affinity chromatography, salt/glycine precipitation, and two virus inactivation steps (solvent/detergent and heat treatment).[15] The von Willebrand Factor:ristocetin co-factor activity (VWF:RCo) is standardized and individual values are provided for each batch. The concentrate is characterized by a high content in VWF, with a mean (SD) VWF:RCo/FVIII:C ratio of 1.58 (0.20).[16]

Patients

This retrospective study involved patients with VWD followed up at their reference center from January 2011 to December 2017. The protocol was approved by the competent authorities in March 2019 and the study was conducted at the haematology departments of 14 Spanish centers according to current standard

clinical practice. Descriptive data on the efficacy and safety of Fanhdi® were collected from patients' medical records between July 2019 and February 2020, and were recorded in an electronic case report form.

Patients were eligible for the study if they were compliant with the following inclusion criteria: patients of both sexes diagnosed with congenital VWD, according to International Society of Thrombosis and Haemostasis [ISTH] criteria,[20] who have received treatment with Fanhdi® as part of standard clinical practice during the study period, and with the minimum data available for analysis (ie, at least one set of baseline and post-treatment data, and one safety data record). Patients were excluded from the study if they were not compliant with any of the inclusion criteria.

Data Collection

Demographics and clinical baseline data were collected including VWD familiar history, levels of factor VIII activity (FVIII:C), VWF:RCo, von Willebrand Factor antigen (VWF:Ag), von Willebrand Factor collagen binding assay (VWF:CB), previous exposure to any VWF concentrate and presence of VWF inhibitors. Bleeding episodes were classified by type, spontaneous or traumatic, and were defined by anatomical site. Surgery procedures were classified as major or minor and the time between start of treatment and surgery was recorded. In major surgeries, it was likely that patients required more than three days of substitutive therapy, while in minor surgeries, less than three days of substitutive therapy was expected, and probably treatment with one or two doses was enough.

Efficacy Assessment

The primary endpoint was to assess the efficacy of pdVWF/FVIII concentrate treatment in three clinical situations: bleeding episodes, prevention of surgical bleeding and secondary long-term prophylaxis. For each clinical situation, efficacy in achieving haemostasis was analysed by describing the clinical variables of the episodes and according to the efficacy scale at the investigator's discretion: (1) Excellent, haemostasis comparable to expectation, with no other associated bleeding cause and no increase of pdVWF/FVIII dose (2) Good, slightly below expectation, with no other associated bleeding cause and requiring a low increase in pdVWF/FVIII dose; (3) Poor, reduced haemostasis compared to expectation, with no other associated bleeding cause and requiring a significant increase in pdVWF/FVIII dose; (4) No response, severe bleeding despite pdVWF/FVIII therapy, requiring a significant increase in pdVWF/FVIII dose and/or an alternative therapy to control bleeding.

For secondary long-term prophylaxis, the number of bleeding episodes per year, the length of hospital stays and the number of red blood cells (RBC) transfusions were compared before and after the prophylaxis period to assess if prophylactic treatment reduces bleeding compared to baseline values.

The secondary efficacy endpoint was the treatment characterization for each clinical situation: regimen and duration of the treatment, dose per infusion, episode duration, number of infusions, concomitant treatment, and total dose of the product.

Safety Assessment

Adverse events (AEs) and serious adverse events (SAEs) recorded in the medical histories were encoded according to the Medical Dictionary for Regulatory Activities version 22 (MedDRA®, ICH, Geneva, Switzerland) by system organ class (SOC). If there was causal relationship between the study drug and the event, the AE was labeled as an AR. For all AEs, the following data were recorded: onset date, duration, intensity (mild, moderate, severe), action taken by the physician, and the outcome. Immunogenicity assessment was aimed at determining the occurrence of hypersensitivity, infusion reactions, alloimmunity, and inhibitor development. Thrombogenicity was assessed by the occurrence of thrombotic events associated with Fanhdi®.

Sample Size

The estimated sample size was the approximate number of patients in Spain who may have been treated with Fanhdi® during the study period. All efficacy analyses were performed on a single sample of assessable patients who met all the inclusion criteria. Safety population consisted of enrolled patients who were treated as part of standard clinical practice and who met inclusion criteria.

Statistical Analysis

Categorical variables were presented by absolute and relative frequencies. Continuous variables were described using means, standard deviations, medians, 25^{th}-75^{th} interquartile (IQR) ranges, and mean 95% confidence intervals (CI). Efficacy variables were analysed using paired Student's t or non-parametric tests (U Mann-Whitney), when applicable. Statistical significance was set as $p < 0.05$. SAS software, version 9.4 (SAS, Cary, NC, USA) was used for statistical analyses.

Results

Baseline Patient Characteristics and Disease Activity

Seventy-two of the 83 recruited patients with VWD met the inclusion criteria and were the evaluable population for the study. Fanhdi® was used in a total of 227 episodes: for treating bleeding (140 episodes, n = 41 patients), for the prevention of surgical bleeding (69 episodes, n = 43 patients), and for secondary long-term prophylaxis (18 programs, n = 13 patients) (Figure 1).

Baseline patient characteristics are shown in Table 1. Overall, of the 72 assessable patients, 28 were male (38.9%) and 44 female (61.1%). Most were adults (median [IQR] age 32 [4-89] years), and the main VWD types diagnosed were

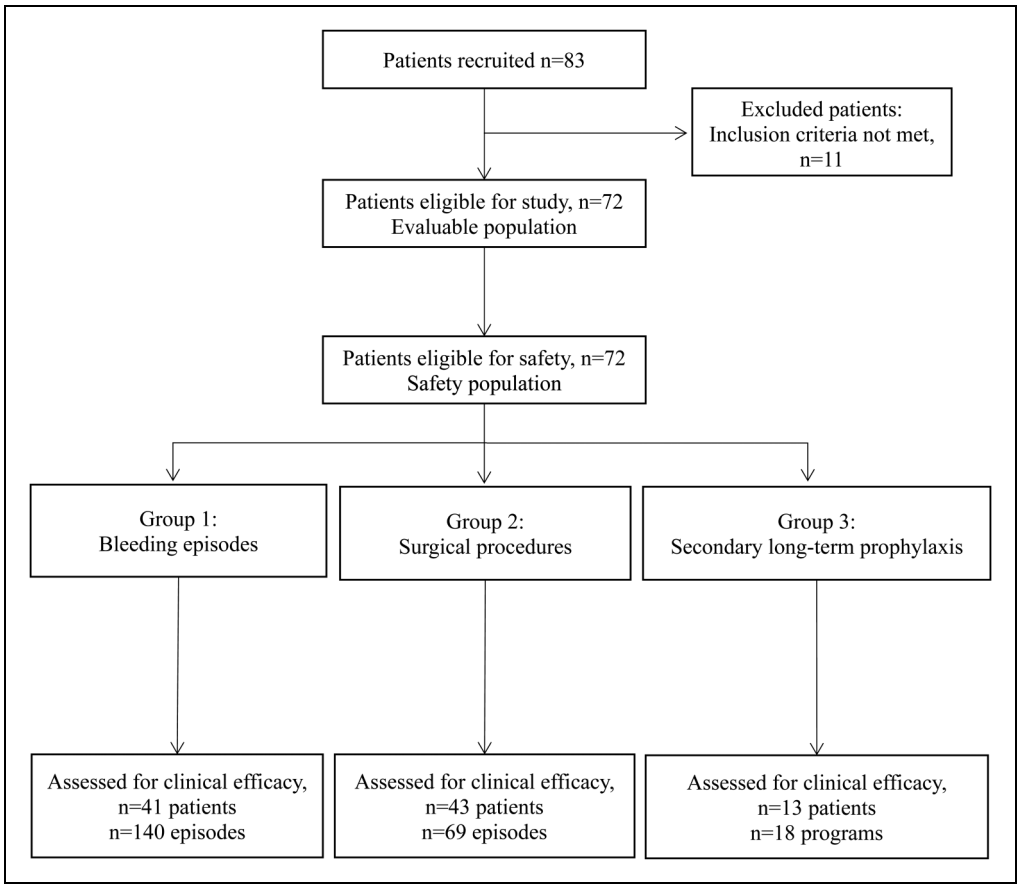

Figure 1. Flow diagram showing the distribution of patients in the study. Two different populations comprised the study: evaluable and safety populations.

Table 1. Demographic and baseline patient characteristics.

		Type of VWD Diagnosed				
			Type 2, n = 28[a]			
	TOTAL, n = 72	Type 1, n = 18	Type 2A, n = 17	Type 2B, n = 6	Type 2N, n = 3	Type 3, n = 26
Demographic						
Sex, *male/female*	28/44	8/10	7/10	2/4	1/2	9/17
Age, *years*	32 (16.5-50)	39 (20-66)	35 (22-60)	33 (14-38)	21 (18-36)	24 (12-37)
Weight, *kg*	64 (48-75)	65 (58-79)	62 (48-75)	66.5 (54-79)	53.1 (36-67.5)	52.9 (31.60-68.50)
Clinical data						
Positive VWD familiar history, *n (%)*	30 (41.7)	6 (33.3)	6 (35.3)	2 (33.3)	0 (0.0)	14 (53.8)
FVIII:C, *IU/dL*	25 (5-48)	44 (20-64.2)	48 (23.5-52)	42 (28-52)	36.3 (26-39)	4 (1.9-13.6)
VWF:RCo, *IU/dL*	12.8 (4.2-23.9)	22.9 (10.4-40.7)	13.7 (4.2-16)	17 (15-27.7)	87 (75-160)	3.3 (0.85-8.75)
VWF:Ag, *IU/dL*	16 (6.8-38.25)	16 (11.6-40)	30.7 (20.85-39.95)	31 (19-37.5)	81 (77-182)	3.1 (0.95-9.95)
VWF:CB, *IU/dL*	6.5 (3-168.5)	n/a	6.5 (6-7)	n/a	65 (65-65)	6 (0-272)
Previous exposition VWF concentrate, *n (%)*	28 (38.9)	5 (27.8)	3 (17.6)	1 (16.7)	1 (33.3)	17 (65.4)
Previous VWF inhibitors, *n (%)*	1 (1.4)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.8)

[a]Type 2M, n = 0; Percentages based on n = 72 assessable patients. There were two patients with type 2 diagnosed, but with subtype not reported. Data are expressed are n (%) or median (IQR). FVIII:C, factor VIII activity; VWF:RCo, von Willebrand Factor:ristocetin co-factor activity; VWF:Ag, von Willebrand Factor antigen; VWF:CB, von Willebrand Factor collagen binding assay. n/a: not available.

Table 2. Management of bleeding episodes according to VWD types diagnosed.

	VWD type[a], *n (%)*					Treatment, *median (IQR)*						
	All	Type 1	Type 2A	Type 2B	Type 3	Episode duration[b], *days*	Treatment duration[c], *days*	Infusions	Median dose, *IU/Kg*	Total dose, *IU*	Concomitant treatment, *n (%)*	Outcome, Excellent/Good, *n (%)*
All bleeding episodes	140 (100)	19 (13.6)	35 (25)	11 (7.9)	67 (47.9)	2 (1-6)	2 (1-6)	2 (1-6)	39 (30-50)	2500 (1500-11000)	60 (42.9)	138 (98.6)
By type												
Spontaneous	106 (75.7)	13 (68.4)	29 (82.9)	8 (72)	48 (71.6)	2 (1-6)	2 (1-8)	2 (1-7)	40 (30-50)	3000 (2000-12000)	45 (42.5)	105 (99)
Traumatic	34 (24.3)	6 (31.6)	6 (17.1)	3 (27.3)	19 (28.4)	1 (1-5)	1 (1-4)	1 (1-4)	37 (30-47.6)	2000 (500-4000)	15 (44.1)	33 (97)
By anatomical site												
Epistaxis	45 (32.1)	7 (36.8)	17 (48.6)	1 (9.1)	20 (29.9)	1 (1-3)	1 (1-2)	1 (1-2)	48 (40-50)	2000 (1500-3000)	17 (37.8)	45 (100)
Gastrointestinal bleeding[d]	22 (15.7)	4 (21.1)	8 (22.9)	0 (0)	2 (3)	3 (2-10)	15.50 (6-36)	11 (6-18)	31.25 (26-39)	18250 (6000-33000)	10 (45.5)	21 (95.5)
Gingival bleeding	21 (15)	3 (15.8)	4 (11.4)	4 (36.4)	10 (14.9)	1 (1-2)	1 (1-2)	1 (1-2)	32.5 (30-37)	2000 (1500-2500)	9 (42.9)	21 (100)
Muscular haematoma	17 (12.1)	0 (0)	1 (5.9)	3 (17.6)	13 (76.5)	7 (1.5-11.5)	8 (2-10)	8 (2-10)	50 (50-59)	12000 (4000-30000)	10 (58.8)	17 (100)
Joint hemarthrosis	9 (6.4)	0 (0)	2 (5.7)	0 (0)	7 (10.4)	10 (5-17)	6 (2-17)	6 (3-10)	37 (30-37.7)	12000 (2500-35000)	4 (44.4)	9 (100)
Other haematomas	5 (3.6)	1 (5.3)	0 (0)	0 (0)	4 (6)	8.5 (5.5-12)	4 (4-4)	4 (4-4)	34.5 (29-43)	2000 (2000-4000)	2 (40)	5 (100)
Menorrhagia	2 (1.4)	0 (0)	0 (0)	0 (0)	2 (3)	3 (1-5)	2.5 (1- 4)	3.5 (1-6)	30 (30-30)	10000 (2000-18000)	2 (50)	2 (100)
Other[e]	19 (13.6)	4 (21.1)	3 (8.6)	3 (27.3)	9 (13.4)	n/a	n/a	n/a	n/a	n/a	n/a	n/a

[a]No patients with subtype 2M and subtype 2N reported any bleeding episode.
[b]Episode duration was calculated by number of days between the end and the start date of the episode.
[c]Treatment duration was calculated as the number of days between the end and the start of the treatment.
[d]There were eight gastrointestinal bleeding episodes related to one patient whose subtype 2 was not reported.
[e]List of n = 19 other localizations reported: birth (n = 2); bleeding in surgical wound (n = 2), contusion (n = 2), haemorrhagic corpus luteal (n = 1), caesarean (n = 1), swelling (n = 2), tongue bleeding (n = 2), tonsil (n = 2); haemoptysis (n = 1), muscular stretch (n = 1), oral mucosa (n = 1), head trauma (n = 1) and upper eyelid (n = 1).
Data are expressed as n (%) or median (IQR). Percentages based on number of cases in each row. n/a: not available.

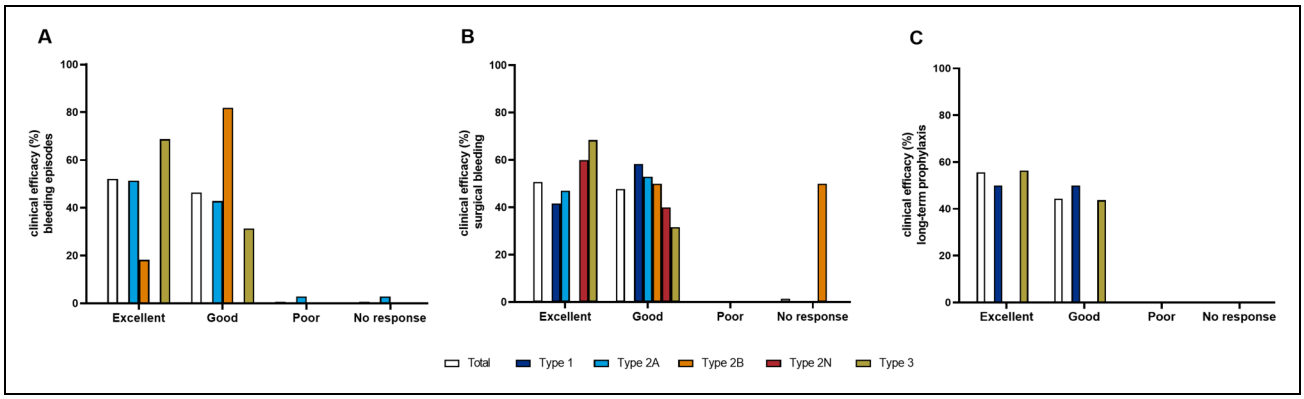

Figure 2. Global clinical efficacy of treatment (%) with Fanhdi® in bleeding episodes, surgeries and secondary long-term prophylaxis, in total study cohort and according to type VWD diagnosed. Total number of episodes reported for (A) bleeding were Excellent (n = 73), Good (n = 65), Poor (n = 1) and No response (n = 1); for (B) prevention of surgical bleeding: Excellent (n = 35), Good (n = 35), and No response (n = 1) and for (C) secondary long-term prophylaxis: Excellent (n = 10) and Good (n = 8).

type 3 (36.1%), type 1 (25%) and subtype 2A (23.6%). One type 3 VWD patient was under treatment with Fanhdi® as part of standard clinical practice and developed inhibitors against VWF prior to study initiation. After immune tolerance induction success, inhibitors were eradicated, and the patient continued on-demand treatment with Fanhdi®.

Bleeding Episodes

Forty-one patients were treated for a total of 140 bleeding episodes. Almost half of the registered bleeding episodes (47.9%) corresponded to type 3 VWD patients. Most of the bleeding episodes (75.7%) were spontaneous and the rest (24.3%) were traumatic. The most frequent localization was epistaxis (n = 45, 32%), followed by gastrointestinal (n = 22, 15.7%) and gingival bleeding, (n = 21, 15%) (Table 2).

The treatment of bleeding episodes lasted a median of two days and 2 (1-6) infusions. Treatment duration of gastrointestinal bleeding was extended beyond the episode duration to prevent any possible recurrent bleeding. Patients were treated with 39 (30-50) IU/Kg of pdVWF/FVIII concentrate and the median dose per patient/year was 50 (35-118 IU/Kg). Sixty (42.9%) bleeding episodes required concomitant treatment: iron, antifibrinolytic preparations and RBC concentrates (Table 2). Remarkably, only three units of RBC concentrates were used.

Overall, global clinical efficacy of the treatment achieved an excellent rating in 52.1% (73 episodes), good in 46.4% (65 episodes), poor in 0.7% (1 episode) and no response in 0.7% (1 episode) (Figure 2A). Importantly, efficacy in type 3 VWD patients was rated as excellent (68.7%), and good in 31.3% of the episodes. Two episodes (1.4%) were classified as poor or no response to the treatment, in two type 2A VWD patients.

Prevention of Surgical Bleeding

Forty-three patients were treated with pdVWF/FVIII concentrate for the prevention of surgical bleeding in 69 instances (major surgery, n = 20; minor surgery, n = 49) (Table 3). The 34.8% of the patients were diagnosed with type 1 VWD, while 34.7% corresponded to type 2 VWD and 27.5% were type 3 VWD. The main surgical procedures reported were tooth extraction (n = 15), arthrocentesis (n = 3), caesarean section (n = 3), colonoscopy with biopsy (n = 3), maxillofacial surgery (n = 3) and vaginal birth with episiotomy (n = 3).

In major surgeries, the median preoperative dose was 40 (33-50) IU/Kg. Median drug exposure after major surgery was 4.5 (2-8.5) days and patients were treated with a median postoperative dose of 40 (30-50) IU/Kg of pdVWF/FVIII concentrate. Patients who underwent minor surgery procedures were treated with a median preoperative and postoperative dose of 30 IU/Kg and a shorter drug exposure, 1 (1-3) days, than in major surgeries. Twenty-nine (42.6%) episodes of surgical bleeding required concomitant treatment: RBC concentrates, iron, antifibrinolytic and antithrombotic preparations. Remarkably, only two units of RBC concentrates were used.

Overall, global clinical efficacy of treatment with Fanhdi® for the prevention of surgical bleeding yielded 50.7% excellent ratings in 35 procedures, 47.8% good ratings in 33 procedures and 1.4% no response ratings in one procedure. Remarkably, in type 3 patients, the percentage of patients with an excellent and good response reached 68.4% and 31.6%, respectively (Figure 2B). One episode (1.4%) was rated as no response in the prevention of surgical bleeding, in a type 2B patient.

Efficacy Assessment on Secondary Long-Term Prophylaxis

Thirteen patients were treated in 18 secondary long-term prophylaxis programs (Table 4). Eleven patients (84.6%) were diagnosed with the severe form, type 3 VWD, and two patients (15.4%) were type 1. The main reasons for initiating the prophylaxis programs were acute bleeding control (28%), pregnancy (28%) and hemarthrosis (17%). The most common bleeding locations (in >5% of the cases) were epistaxis

Table 3. Prevention of surgical bleeding according to type of VWD diagnosed.

		VWD type[a], *n (%)*					Treatment, *median (IQR)*					
	All	Type 1	Type 2A	Type 2B	Type 2N	Type 3	Preoperative dose, *IU/Kg*	Treatment duration, *days*	N° of infusions	Median postoperative dose, *IU/Kg*	Total dose, *IU*	Concomitant treatment[b], *n (%)*	Outcome, Excellent/ Good, *n (%)*
All surgical bleeding	69 (100)	24 (34.8)	17 (24.6)	2 (2.9)	5 (7.2)	19 (27.5)	35 (30-45)	1 (1-5)	3 (1-7)	32.3 (24.2-40)	3000 (2000-9500)	29 (42.6)	68 (98.6)
Classification													
Major	20 (29)	6 (30)	5 (25)	1 (5)	2 (10)	5 (25)	40 (33-50)	4.5 (2-8.5)	5 (2.5-8)	40 (30-50)	9000 (3000-19500)	8 (40)	20 (100)
Minor	49 (71)	18 (36.7)	12 (24.5)	1 (2)	3 (6.1)	14 (28.6)	30 (24.2-41.7)	1 (1-3)	2 (1-4)	30 (24-35)	3000 (2000-7500)	21 (43.8)	48 (98)

[a]There were no patients with subtype 2M diagnosed and two patients with subtype not reported.
[b]There was one major surgical bleeding with use of concomitant treatment not reported.
Data are expressed as n (%) or median (IQR). Percentages based on number of cases in each row.

(39.6%), gingival (22.9%), joints (10.4%) and gastrointestinal (8.3%). The pdVWF/FVIII concentrate regimen was 3 days/ week in 66.7% of patients with a median (IQR) treatment duration of 119 (67-433) days. Patients received a median dose per infusion of 2000 (1088-3000) IU of Fanhdi®.

There were no statistically significant differences between the mean (SD) number of bleeding episodes per year before (1.3 [1.6]; n = 14) and during the secondary long-term prophylaxis periods (0.6 [1.1]; n = 14) (absolute change 0.7 [2]; 95% CI [-0.43, -1.87]; $P = 0.20$). Hospital stay duration was not significantly different between the year before prophylaxis (0.7 [2.2] days; n = 10) and during the prophylaxis period (0.9 [2.8] days; n = 10). Similarly, the number of RBC transfusions revealed no differences between the groups.

Overall, global clinical efficacy of Fanhdi® was excellent in the 55.6% of the secondary-long term prophylaxis programs (n = 10) and good in the 44.4% of them (n = 8) (Table 4). Efficacy of treatment in type 3 VWD patients yielded an excellent and good efficacy ratings of 50% each, similar to the overall efficacy in the whole study cohort (Figure 2C).

Safety Assessment

Overall, there was a total of 15 AEs, reported by eight (11.1%) patients during the study period. By intensity, only three AEs (23.1%) were reported as severe: anaemia (n = 2) and infectious mononucleosis (n = 1), while the rest of them (76.9%) were mild or moderate. Most common AEs by SOC were gastrointestinal disorders (33.3%), infections and infestations (20%), blood and lymphatic system disorders (13.3%) and respiratory system disorders (13.3%). There were no patients who discontinued or reduced their dose due to an AE and all patients recovered without complications. All AEs with known outcomes were non-related to study drug, therefore no patients experienced a confirmed AR. No deaths were reported during the study period. Five AEs were related to immunogenicity, being infections and infestations (n = 3) and respiratory disorders (n = 2). No thrombotic events were associated with the use of Fanhdi®.

Discussion

We investigated the use of a pdVWF/FVIII concentrate, Fanhdi®, in standard clinical practice over a period of seven years in 72 well-characterized patients. This large retrospective study was conducted in 14 centers in Spain and proved that the concentrate was safe and effective for treating bleeding episodes, prevention of surgical bleeding, and for secondary long-term prophylaxis in a real-world setting.

In our study, the patient distribution was well-balanced among all VWD types: type 1, 25%; type 2, 39% and type 3, 36%. Although the prevalence of VWD types 2 and 3 is lower in the general population (20% and <5%, respectively), the higher proportion observed in the current study was expected, since eligible patients were those treated with a pdVWF/FVIII concentrate. In our study, two (2.8%) patients presented previous alloantibodies against VWF. Although the

Table 4. Clinical data of von Willebrand disease (VWD) patients enrolled into each secondary long-term prophylaxis program.

Patient number	VWD type	Sex	Age	Follow-up, *days*	Reason to prophylaxis	Frequency, *days per week*	Mean dose per infusion, *IU*	Outcome
1	3	F	39	234	Pregnancy	10 days/month	3000	Excellent
				930	Pregnancy	3	3000	Excellent
				699	Pregnancy	3	2721	Excellent
				189	Ovarian cyst	3	1500	Excellent
				81	Haematoma	3	3000	Excellent
				131	Pregnancy	3	3000	Excellent
2	3	M	58	219	Gingivorrhagia	3	3000	Excellent
3	3	M	34	2095	Acute bleeding control[a]	3	3000	Excellent
4	1	F	8	91	Acute bleeding control[a]	3	500	Excellent
5	1	M	4	193	Acute bleeding control[a]	2	500	Good
6	3	F	9	2515	Acute bleeding control[a]	3	625	Good
7	3	M	20	2556	Acute bleeding control[a]	3	1500	Good
8	3	M	21	220	Hemarthrosis	3	2000	Excellent
9	3	F	32	–	Hemarthrosis	3	2000	Good
10	3	F	49	–	Hemarthrosis	2	2000	Good
11	3	F	26	286	Pregnancy	Every other day	2000	Good
12	3	F	9	2771	Other[b]	1	1088	Good
13	3	F	8	1638	Other[b]	2	500	Good

[a]Acute bleeding control is referred to the following locations: epistaxis (n = 3), digestive tract (n = 2), head skin wound (n = 1), gingival bleeding (n = 1) and lip wound (n = 1).
[b]Other is referred to the following locations: gastrointestinal (n = 2), vaginal bleeding (n = 1), and frontal haematoma (n = 1).

exposure to a VWF/FVIII concentrate may be associated with allergic events and lack of hemostatic response in these patients,[21] these clinical events were not identified.

In patients treated for bleeding episodes, global clinical efficacy was achieved in the 98.5% of the cases (excellent, 52.1%; good, 46.4%). Clinical responses rated as excellent increased to 68.7% in type 3 patients. This result supports the use of the pdVWF/FVIII concentrate in patients with severe forms of VWD who are at a greater risk of experiencing life-threatening bleeding. As expected, epistaxis and gingival bleeding needed the fewest number of infusions, whereas gastrointestinal bleeding, muscular haematomas and joint hemarthrosis required higher numbers. In all cases, this treatment regimen effectively controlled bleeding episodes and the haemostatic effect was similar to that reported elsewhere.[11,12,16,17] Overall, patients required a median dose of 39 IU/Kg to stop bleeding after following standard recommended dosages for this indication.[4,8]

The efficacy of Fanhdi® was also assessed in major and minor surgeries. Clinical efficacy was rated as excellent (50.7% of procedures), and good (47.8% of procedures), yielding a total efficacy of 98.5% in these surgical procedures. Similarly, previous retrospective studies with pdVWF/FVIII concentrates showed comparable efficacy rates.[12,15,17,22] Remarkably, in type 3 VWD patients, clinical efficacy rated as excellent increased up to 68.4%. This finding supports the use of pdVWF/FVIII concentrate replacement therapy in those patients who are lacking VWF and are unresponsive to DDAVP. In agreement with the recommended dosages for the management of bleeding in surgical procedures,[1] the pdVWF/FVIII postoperative doses for major and minor surgeries were 40 IU/Kg and 30 IU/Kg, respectively.

Although secondary long-term prophylaxis is not the current standard of care in VWD, it is currently recommended for patients with severe VWD and frequent bleeds[23,24] to avoid the development of arthropathies and to improve quality of life.[14,16,18,25] Here, we reported an efficacy rate of excellent/good in 100% of the prophylaxis programs in severe VWD patients. No secondary prophylaxis programs were rated as poor or no response. Additionally, most of these patients were diagnosed with the severe form, type 3 VWD. Fanhdi® was administered three times per week to control bleeding.

Patient's bleeding history is a critical step to define the severity of a bleeding disorder.[26] The use of secondary long-term prophylaxis with pdVWF/FVIII concentrates in type 3 VWD patients has shown a reduction in ABR for epistaxis, gastrointestinal, joint bleeding and menorrhagia.[14,16,18] However, our results did not reveal either a reduction in the number of bleeding episodes per year or in hospital stay duration. This could be explained by the small sample size of the cohort included in secondary prophylaxis programs, and considering the observed absolute decrease in the number of bleeding episodes per year, a clinical effect could be confirmed in a larger population. Furthermore, our study population did not show a frequent bleeding phenotype, as measured by the number of

bleeding episodes (1.3 episodes/year) compared with patients from previous trials, who showed one bleeding episode per month,[14] or three or more recurrent bleeds at the same site.[25] Despite the low frequency of bleeding episodes, secondary long-term prophylaxis was deemed necessary since many patients with type 3 severe form of VWD may develop gastrointestinal and joint bleeding, and prophylaxis should be initiated before joint disease development.[27]

Regarding safety, Fanhdi® showed a good safety profile which aligned with reports for other pdVWF/FVIII concentrates.[22] There were no AEs, SAEs or discontinuations related to the pdVWF/FVIII concentrate. The most common AEs were mild to moderate gastrointestinal disorders. As VWF facilitates platelet aggregation and thrombus formation, it has been suggested that there might be an increased risk associated with venous thrombosis after repeated infusions.[28,29] Notably, there were no thrombotic events associated with the use of the study drug. Regarding immunogenicity, 5 to 10% of type 3 VWD patients may develop alloantibodies against VWF presenting as a lack of haemostatic response or even anaphylactic reactions.[21] Remarkably, immunogenicity related AEs were mainly mild infections and respiratory disorders, not associated with inhibitor development, hypersensitivity or infusion reactions. Altogether, safety results confirmed that the pdVWF/FVIII concentrate was well tolerated in VWD patients.

One of the strengths of this real-world evidence study is that supports the use of Fanhdi® in a more representative and realistic population than in a randomized controlled trial, and demonstrated the product safety and effectiveness in standard clinical practice. In addition, we showed the breakdown of efficacy in terms of excellent and good responses, whereas previous studies using pdVWF/FVIII concentrates reported excellent/good responses lumped together.[16,30,31] Limitations of the study must be acknowledged. First, the small sample size of the cohort of patients included in secondary prophylaxis programs made it difficult to generate robust results. Second, due to the retrospective nature of the study, some data such as the subtype of VWD reported, or specific AE characteristics, were missing in some patients. Third, the study intended to include PK values such as FVIII:C activity, VWF:RCo, and VWF:Ag levels for each clinical situation. Unfortunately, these data were not available to perform a formal analysis.

Conclusion

Fanhdi®, a highly purified pdVWF/FVIII concentrate with a high content of active VWF, has been proven to be effective, safe and well-tolerated in the management of bleeding episodes, the prevention of excessive bleeding during major and minor surgical procedures, and for secondary long-term prophylaxis in patients with VWD in Spain.

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Author Contribution

V. Jiménez-Yuste: conceptualization, methodology, data curation, resources, formal analysis and investigation; R. Mir: conceptualization, project administration, supervision, and visualization; M.T. Alvarez-Román, O. Benitez Hidalgo, N.F. Pérez González, R. Núñez, J.R. Gonzalez-Porras, C. Marzo, M. J. Varó Castro, A. Palomo Bravo, C. Hernández-García, J. Coll, M. Carrasco, M.M. Nieto Hernández, F. García Candel, and B. J. Galmes: data curation, investigation and resources. All authors critically revised, edited and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: R. Mir is full-time employee of Grifols and has no other competing interests to declare. V. Jiménez-Yuste received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or honoraria for consulting, and/or funds for research from Shire, Bayer, CSL-Behring, Grifols, Novo Nordisk, Sobi, Octapharma, BioMarin, Sanofi and Pfizer. M.T. Alvarez-Román received reimbursement for attending symposia and/or honoraria for speaking and/or honoraria for consulting, and/or funds for research from Takeda, Bayer, CSL-Behring, Grifols, Novo Nordisk, Sobi, Octapharma, BioMarin, Novartis, Amgen and Pfizer. O. Benítez Hidalgo received reimbursement for attending symposia/congresses and/or honoraria for speaking and/or advisory boards from Bayer, CSL-Behring, Takeda, Sobi and Pfizer. R. Núñez reports personal fees or consulting services for Novonordisk, Bayer, Takeda, Roche, Pfizer, CSL Behring and Sobi. J.R. Gonzalez-Porras reports financial activities outside the submitted work: fees for consulting services by Amgen, Novartis, Sobi, Grifols, and CSL Behring, and speaking honoraria from NovoNordisk, Shire, Sobi, Roche, Daiichi Sankyo, Pfizer, Amgen, Novartis. N.F. Pérez González, C. Marzo Alonso, A. Palomo Bravo, C. Hernández García, J. Coll, M. Carrasco, M.M. Nieto Hernández, B. J Galmes, M.J. Varó Castro and F. García Candel have no conflict of interest to declare.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Presentations at Meetings

The manuscript has been presented, in the form of an abstract, at the meetings EAHAD Feb 5 to 7, 2020 and ISTH July 12 to 14, 2020, and presented orally at the SETH/SEHH congress Oct 20 to 24, 2020.

Ethical Approval

Ethical approval to report this study was obtained from the ethics committee of Hospital Universitario la Paz (ID number: HULP PI-3597).

Informed Consent

Informed consent for patient information to be published in this article was not obtained because of the retrospective nature of the study.

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