Human von Willebrand factor/factor VIII concentrates in the management of pediatric patients with von Willebrand disease/hemophilia A

Giancarlo Castaman
Silvia Linari
Department of Oncology, Center for Bleeding Disorders, Careggi University Hospital, Florence, Italy

Abstract: Several plasma-derived intermediate and high-purity concentrates containing von Willebrand factor (VWF) and factor VIII (FVIII) are currently available. The main role of these products in the management of the pediatric population is represented by the replacement therapy in patients with severe or intermediate forms of von Willebrand disease, in whom other treatments are ineffective or contraindicated. Another important role of VWF/FVIII concentrates in children may be their use in immune tolerance induction (ITI) protocols. ITI is particularly recommended for hemophilia A children who have developed an inhibitor against FVIII, currently the most serious complication of substitutive treatment in hemophilia. Although recombinant concentrates may represent the preferred option in children with hemophilia A, VWF/FVIII concentrates may offer an advantage in rescuing patients who failed previous ITI.

Keywords: von Willebrand factor, factor VIII, plasma-derived concentrates, children, von Willebrand disease, hemophilia A

Introduction
Several plasma-derived intermediate and high-purity concentrates containing von Willebrand factor (VWF) and factor VIII (FVIII) are available. VWF is a large multimeric adhesive plasma glycoprotein, composed of a series of dimers of mature subunits, that has an essential role in both primary and secondary hemostasis. Biosynthesis of VWF is restricted to megakaryocytes and endothelial cells. Its primary function is to promote platelet adhesion to subendothelium exposed by vascular injury. VWF also cooperates with fibrinogen in platelet–platelet interactions, promoting thrombus growth and stabilization. A second critical role for VWF is to act as the carrier protein for coagulation FVIII in plasma, protecting it from early proteolytic degradation. This pleiotropic function of VWF can be evaluated using different laboratory assays because no single test covers the entire spectrum of VWF activities (Table 1). The deficiency or abnormality of VWF causes von Willebrand disease (VWD), the most frequent autosomal inherited bleeding disorder in humans. FVIII is crucial for coagulation, and its deficiency causes hemophilia A (HA), an X-linked bleeding disorder characterized by a life-long bleeding disorder whose severity is closely associated with the severity of FVIII deficiency in plasma.

The aim of the present review is to highlight the current role of human VWF/FVIII concentrates in the management of pediatric patients with VWD and HA.

Current human VWF/FVIII concentrates
Different human VWF/FVIII products are available for replacement therapy. These concentrates were initially introduced in clinical practice for the treatment of HA.
All currently available VWF/FVIII concentrates are plasma derived; however, very recently, a recombinant VWF concentrate (vonvocog alfa; BAX 111, licensed under the trade name Vonvendi; Baxalta US Inc., Westlake Village, CA, USA) has been approved by Food and Drug Administration (US FDA) in December 2015 for on-demand treatment and control of bleeding episodes in adults with VWD.\(^6\)\(^7\)

Plasma-derived concentrate production depends on plasma donor availability, and despite viral screening and virucidal methods developed to minimize such concerns, the theoretical risk of blood-borne infection transmission cannot be excluded.\(^8\) Several procedures contribute to the viral safety of plasma-derived concentrates, including the quarantine of plasma undergoing industrial fractionation and obtained from regular well-surveyed donors and the introduction of nucleic acid amplification testing for five viruses (HIV 1–2, HBV (hepatitis B virus), HCV (hepatitis C virus), hepatitis A virus, and parvovirus B19). Furthermore, virucidal or removal techniques such as dry heating, pasteurization, vapor and solvent/detergent procedures, and ultrafiltration and nanofiltration steps contribute further to guarantee the safety of the final plasma-derived products. All coagulation factor concentrates are subjected to different methods of viral inactivation, attenuation, or elimination. Actually, plasma-derived concentrates maintain a high safety profile. However, vaccination against hepatitis B and A viruses should be offered to candidates for replacement treatment, if not already done through health programs.\(^9\)

VWF/FVIII concentrates show a variable VWF and FVIII content and a heterogeneous multimer pattern (Table 2).\(^10\) However, the concentration of functional VWF may vary significantly, as supported by the wide difference in VWF:ristocetin cofactor (RCO)/VWF:antigen (Ag) ratio. Also, the ratio of VWF activity to FVIII:C content varies and this results in significantly different levels of the two proteins achieved post-infusion. Nowadays, most concentrates are labeled for their FVIII and VWF:RCO content, and appropriate and hemostatically safe replacement treatment can be planned.\(^11\)\(^12\) VWF concentrates

| Table 1 Laboratory assays for VWF activities\(^{15}\) |
|----------------|-----------------|
| **Test** | **Pathophysiological significance** |
| Antigen of VWF (VWF:Ag) | Antigen concentration |
| Ristocetin cofactor activity of VWF (VWF:RCO) | VWF–GPib interaction as mediated by ristocetin in vitro |
| Factor VIII procoagulant activity (FVIII:C) | FVIII–VWF interaction |
| Bleeding time (IVY method) | Platelet–vessel wall VWF-mediated interaction |
| Binding of VWF to collagen (VWF:CB) | VWF–collagen interaction |
| Binding of FVIII to VWF (VWF:FVIII:C) | FVIII–VWF interaction |
| Multimer analysis | Threshold ristocetin concentration inducing patient’s platelet-rich plasma aggregation |
| Closure time PFA-100 | Multimer composition of VWF |
| Propeptide assay (VWFpp) | Simulates primary hemostasis after injury to a small vessel |
| Measures the amount of VWF–pp released in plasma |


**Abbreviations:** VWF, von Willebrand factor; Ag, antigen; RCo, ristocetin cofactor; GPib, glycoprotein Ib; FVIII, factor VIII; RiPA, ristocetin-induced platelet aggregation; PFA, Platelet Function Analyzer.

| Table 2 VWF/FVIII concentrates licensed in Europe |
|----------------|-----------------|-----------------|-----------------|-----------------|
| **Product** | **Brand** | **Purification** | **Viral inactivation** | **VWF:RCO/Ag content (ratio ± SD)** | **VWF:RCO/FVIII content (ratio ± SD)** |
| Alphanate | Grifols | Heparin ligand chromatography | S/D + dry heat (80°C, 2 h) | 0.47±0.1 | 0.91±0.2 |
| Factor 8Y | Bio Products Laboratory | Heparin/glucose precipitation | Dry heat (80°C, 72 h) | 0.29 | 0.82 |
| Fanhdi | Grifols | Heparin ligand chromatography | S/D + dry heat (80°C, 72 h) | 0.47±0.1 | 1.04±0.1 |
| Haemate P | CSL Behring | Multiple precipitation | Pasteurization (60°C, 10 h) | 0.59±0.1 | 2.45±0.3 |
| Immunate | Baxter | Ion exchange chromatography | S/D + vapor heat (60°C, 10 h) | 0.47 | 1.1 |
| Wilate | Octapharma | Ion exchange + size exclusion chromatography | S/D + dry heat (100°C, 2 h) | – | 0.9 |
| Wilfactin | LFB | Ion exchange + affinity | S/D, 35 nm filtration, dry heat (80°C, 72 h) | 0.95 | 50 |

**Abbreviations:** VWF, von Willebrand factor; FVIII, factor VIII; S/D, solvent/detergent; RCo, ristocetin cofactor; Ag, antigen.
differ with regard to production techniques, so that the retention or loss of high molecular weight (HMW) VWF may vary broadly.\textsuperscript{10} It has already been suggested that HMW VWF multimers represent the most adhesive functional forms of VWF, so that a HMW-containing VWF concentrate would theoretically provide more hemostatic efficacy.

The current indications for VWF:FVIII concentrates in children are replacement therapy in VWD and immune tolerance induction (ITI) therapy in HA with inhibitors.

**Human VWF/FVIII concentrates in the management of pediatric patients with VWD**

VWD is the most frequent inherited bleeding disorder, reaching a prevalence of ~1% in pediatric populations.\textsuperscript{13} However, clinically relevant cases referred to specialized centers have a tenfold lower prevalence.\textsuperscript{14} The disorder is caused by the quantitative and/or qualitative abnormalities of VWF and is mainly transmitted in an autosomal dominant manner. VWD is a very heterogeneous disease and is classified into three main types according to quantitative (type 1 and 3) or qualitative (type 2A, 2B, 2M, and 2N) VWF abnormalities (Table 3).\textsuperscript{15,16} Type 1 is the most common form of VWD; it is characterized by an equivalent mild to moderately severe reduction in plasma of both VWF:Ag and VWF:RCo. VWF is functionally normal, as also demonstrated by the presence of all plasma VWF multimers, albeit at a reduced concentration, and plasma levels of FVIII are usually reduced in proportion to VWF. Type 2A is inherited mainly as a dominant trait and is the most frequent qualitative defect of VWF. The laboratory hallmark is a low VWF:RCo/VWF:Ag ratio (<0.6), associated with lack of large and often also of intermediate size VWF multimers, and ristocetin-induced platelet aggregation is severely reduced. Heightened ristocetin-induced platelet aggregation, occurring at ristocetin concentration lower than in normal controls, with mild to moderate thrombocytopenia, mildly reduced to normal FVIII and VWF:Ag, reduced VWF:RCo, and absence of the HMW multimers in plasma are peculiar features of typical type 2B cases, similarly inherited in a dominant manner with high penetrance. In this type, platelet function abnormality may be also present.\textsuperscript{15} In type 2M VWD, VWF multimer distribution is normal, but platelet-dependent VWF activities (VWF:RCo and von Willebrand factor collagen binding activity [VWF:CB]) are disproportionately reduced compared to VWF:Ag. Type 2N is recessively inherited, and patients show normal levels of VWF:Ag and VWF:RCo and a normal multimer pattern. Low plasma levels of FVIII:C (typically 5–40 U/dL) result from the increased clearance of this moiety as a consequence of mutations occurring in the VWF region, which reduce binding of FVIII. Type 3 VWD is rare and recessively inherited. It is characterized by severe bleeding tendency, very low VWF levels (usually <3 U/dL), and FVIII:C reduction similar to what is observed in moderate HA (typically 1–5 U/dL).

The diagnosis of VWD is based on the triad including the presence of a bleeding history, preferably collected through standardized questionnaires, evidence of bleeding tendency in other family members, and reduced VWF:RCo levels in plasma (<40 U/dL). Further characterization of VWD type requires the measurement of VWF:Ag and FVIII:C and the analysis of multimer pattern.\textsuperscript{16,17} VWF levels below 30 U/dL are associated with a more significant clinical severity\textsuperscript{18} and with the likelihood of finding causative mutations in *VWF* gene, mapped at chromosome 12p13.2.\textsuperscript{19} Therefore, the severity of bleeding tendency is usually proportional to the degree of the primary deficiency of VWF and to that of secondary deficiency of FVIII. Mucocutaneous bleeding (easy bruising, epistaxis especially in children, menorrhagia) is frequently reported, often impairing the quality of life and requiring iron treatment for chronic anemia. Since FVIII is usually only mildly reduced, hemorrhaxis and deep muscle hematoma, typical of severe clotting deficiency, are rare apart from type 3 VWD, in which bleeding episodes resemble those of moderate hemophilia. Gastrointestinal bleeding in older patients may be particularly frequent and difficult to manage, especially in patients with type 2 lacking HMW multimers in plasma.\textsuperscript{20} Bleeding after dental extraction is the most frequent postoperative bleeding manifestation, whereas bleeding after surgery may occur in more severely affected type 1 and 3 VWD patients. Since FVIII/VWF levels are

**Table 3 Classification of von Willebrand disease**

<table>
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<th>Quantitative deficiency of VWF</th>
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<tr>
<td>Type 1 Partial quantitative deficiency of VWF</td>
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<tr>
<td>Type 3 Virtually complete deficiency of VWF</td>
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<table>
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<tr>
<th>Qualitative deficiency of VWF</th>
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<tr>
<td>Type 2 Qualitative deficiency of VWF</td>
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<tr>
<td>Type 2A Qualitative variants with decreased platelet-dependent function associated with the absence of high and intermediate molecular weight VWF multimers</td>
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<tr>
<td>Type 2B Qualitative variants with increased affinity for platelet GP Ib</td>
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<tr>
<td>Type 2M Qualitative variants with decreased platelet-dependent function not caused by the absence of high molecular weight VWF multimers</td>
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<tr>
<td>Type 2N Qualitative variants with markedly decreased affinity for FVIII</td>
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**Abbreviations:** VWF, von Willebrand factor; GP Ib, glycoprotein Ib; FVIII, factor VIII.
usually normalized at the end of pregnancy in mild type 1 cases, replacement therapy postpartum to prevent immediate or delayed bleeding is required in females with type 2A, 2B, and 3 VWD.

The aim of therapy in VWD is to correct the dual defect of hemostasis, ie, the abnormal platelet adhesion-aggregation caused by low or dysfunctional VWF and the abnormal intrinsic coagulation owing to low FVIII levels. Two main therapeutic options are available: desmopressin (DDAVP [1-deamino-8-D-arginine-vasopressin]), which releases endogenous VWF from endothelial cells, and exogenous VWF contained in VWF/FVIII concentrates. DDAVP is an analog of the antidiuretic hormone vasopressin, V2 agonist.\(^\text{21}\) The drug is free of risk of viral transmission and inexpensive. DDAVP raises circulating FVIII and VWF levels by three-to fivefold over the patient’s baseline level by stimulating the release of FVIII/VWF from the storage sites in the vascular endothelial cells. DDAVP is the first-choice treatment for patients with type 1 VWD and baseline VWF and FVIII levels higher than 10 U/dL, provided a normal content of VWF in storage compartments.\(^\text{22}\) Variable responses are observed in type 2A and 2M, but typically VWF:RCo is hardly corrected in these types. In type 2B, thrombocytopenia may occur or aggravate because an abnormal VWF with enhanced affinity for platelet GPIb is released leading to an increased risk of bleeding and thus the compound is generally contraindicated.\(^\text{23}\) Patients with type 3 VWD do not respond to DDAVP because of the lack of VWF in storage compartments. DDAVP can be administered intravenously, subcutaneously, or intranasally. DDAVP can be given prior to surgical procedures or for the treatment of acute spontaneous or traumatic bleeding events. DDAVP can be administered every 12–24 hours, but when repeated doses are administered at closely-spaced intervals tachyphylaxis often ensues because of the depletion of VWF/FVIII from the stores. Flushng and mild increase of blood pressure are relatively frequent minor side effects, while retention of free water may induce hyponatremia, especially in infants less than 2 years of age, thus precipitating the onset of seizures. Therefore, close monitoring of these subjects with fluid restriction and serum sodium levels is advised. The occasional episodes of arterial thrombosis during treatment have never been reported in pediatric patients, and DDAVP is best avoided in adults with overt cardiovascular diseases.

When DDAVP is ineffective or contraindicated, replacement therapy with VWF/FVIII concentrates is the treatment of choice to restore VWF and FVIII levels. All these concentrates maintain similar hemostatic efficacy and show similar pharmacokinetics.\(^\text{24-29}\) However, the VWF/FVIII concentrate Haemate\(^{\text{®}}\) P (CSL Behring, King of Prussia, PA, USA) has been widely used in patients with VWD for its particularly high VWF content (VWF:RCo/ FVIII ratio 2.5).\(^\text{30}\) After infusion, the half-life of FVIII:C is approximately twice that of VWF:Ag (20–24 vs 10–14 hours) because of the endogenous increase of FVIII, which is stabilized by providing exogenous VWF.\(^\text{31}\) Replacement of VWF to achieve hemostatically adequate plasma levels for prevention or treatment of acute bleeding is the mainstay of treatment when DDAVP cannot be used. Spontaneous or posttraumatic bleeding should be treated promptly and surgery should be planned to prevent bleeding complications. There are a large number of expert and national guidelines or recommendations for VWD treatment, and although there are similarities in some recommendations, notable differences may exist in practice and the suggestions mentioned in Table 4 may be used to guide treatment.\(^\text{36}\) According to the severity of bleeding episode, a single or daily doses for 2–3 days of 20–50 IU/kg of VWF:RCo are indicated to treat spontaneous or posttraumatic bleeding episodes or prior to invasive procedures in patients with severe VWF deficiency (VWF:RCo levels at baseline below 10 U/dL). For major surgery, the aim is to maintain FVIII plasma level at ~80–100 U/dL for at least 2 days and through level above 50 U/dL for additional 5–7 days. A loading dose of 50 IU/kg of VWF:RCo is usually administered 30–60 minutes before surgery, and similar doses should be given for the next 2 days. After infusion there is an accumulation of FVIII, which is exogenously infused but also normally produced in VWD patients and stabilized by the infused VWF. This may result in a very high plasma FVIII:C concentration when repeated infusions are given, especially to cover major surgery.\(^\text{32}\) There is some concern that sustained high levels of post-infusion FVIII:C may be associated with episodes of deep vein thrombosis in adult VWD patients,\(^\text{33,34}\) but no such cases have been reported in pediatric patients. To guarantee appropriate and safe doses, FVIII:C plasma level should be measured daily to avoid levels greater than 150 U/dL, which is roughly recognized as a the threshold for an increased risk of venous thromboembolism.\(^\text{35}\) Treatment may also be monitored with VWF:RCo assays. Alternatively, a product containing high dose of VWF and very little FVIII (Wilfactin\(^{\text{®}}\); LFB, Les Ulis, France) can be used. However, with this product, post-infusion FVIII:C levels increase slowly with the peak being reached after 6–8 hours. Thus, coadministration of a priming dose of FVIII may be required if prompt hemostasis is needed in patients with baseline FVIII:C levels ≤30 U/dL.\(^\text{36}\) Plasma-derived concentrates
containing VWF are contraindicated in some type 3 VWD patients with homozygous gene deletions or nonsense mutations who develop precipitating alloantibodies causing life-threatening anaphylactic reactions. Recombinant activated factor VII or recombinant FVIII concentrates free of VWF administered by continuous intravenous infusion have been successfully used in these patients.

A human recombinant VWF, vonicog alfa, synthesized by a genetically engineered CHO cell line, has been developed to avoid the risks associated with the use of plasma-derived VWF. Vonicog alfa (BAX 111) has been approved by FDA in December 2015 for on-demand treatment and control of bleeding episodes in adults with VWD. Further clinical trials are ongoing to assess its safety and efficacy in the pediatric population and for prophylaxis.

At variance with what is commonly observed in hemophilia, long-term prophylaxis is rarely used in VWD because of the greater phenotypic heterogeneity. The bleeding pattern is usually milder than in severe hemophilia and irreversible sequelae are not as common. However, some patients with type 3 VWD and FVIII:C levels <10 U/dL may suffer from frequent hemarthrosis, with development of target joints and chronic arthropathy, or recurrent spontaneous gastrointestinal bleeding, often without evidence of grossly anatomical lesions. Pediatric patients can also experience epistaxis frequently and severe enough to cause anemia. Secondary long-term prophylaxis may be useful in these patients, and indeed sporadic clinical experience with secondary long-term prophylaxis in VWD has been successful in case series, although using heterogeneous schedules of administration. Unfortunately, as for hemophilia patients, the impact on already established joint damage is limited and thus prophylaxis for joint bleeding in children with VWD should be started as soon as possible to attenuate the risk of late joint complications. However, prospective trials are needed to better evaluate the cost-effectiveness of this approach and the impact on patient’s quality of life in comparison with on-demand therapy.

**Human VWF/FVIII concentrates in the management of pediatric patients with HA**

HA is an X-linked recessive bleeding disorder caused by mutations in the gene encoding coagulation FVIII. Patients with FVIII plasma levels <1 U/dL are classified as severe hemophiliacs, and they usually suffer from recurrent musculoskeletal bleeding, particularly joint bleeding, as the hallmark of disease. Primary prophylaxis is the regular continuous treatment initiated in the absence of documented osteochondral joint disease and started before the second clinically evident large joint bleeding and the age of 3 years and currently represents the primary goal of FVIII replacement therapy. Primary prophylaxis is the regimen of choice for the treatment of children with severe hemophilia, with

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**Table 4** Suggestions for replacement therapy in VWD

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<tr>
<th>Spontaneous bleeding episodes</th>
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<tr>
<td>• Single or daily doses of 30–60 IU/kg of VWF to maintain FVIII:C levels &gt;30 U/dL until bleeding stops (usually 2–4 days)*</td>
</tr>
<tr>
<td><strong>Major surgery</strong></td>
</tr>
<tr>
<td>• Daily doses of 50–60 IU/kg of VWF to maintain preoperative FVIII:C and VWF:RCo levels of 80–100 U/dL until 36 hours postoperatively and then &gt;50 U/dL until healing is complete (usually 5–10 days)*</td>
</tr>
<tr>
<td>• Measure plasma levels of FVIII:C (and VWF:RCo) every 12 hours on the day of surgery, then every 24 hours</td>
</tr>
<tr>
<td>• LMWH should be used as prophylaxis in patients at high risk of venous thrombosis</td>
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</table>

**Minor surgery**

• Daily or every other day doses of 30–60 IU/kg of VWF to maintain FVIII:C levels >30 U/dL until healing is complete (usually 2–4 days)*

**Dental extractions or invasive procedures**

• Single dose of 30 IU/kg of VWF to maintain FVIII:C levels >50 U/dL for 12 hours*

**Delivery and puerperium**

• Daily doses of 50 IU/kg of VWF to maintain FVIII:C levels >50 U/dL for 3–4 days

**Long-term secondary prophylaxis** with VWF/FVIII concentrates may be considered for patients with severe VWD and recurrent bleeding in dangerous sites (gastrointestinal bleeding, hemarthrosis, epistaxis in children)

**Possible indications for VWF concentrates devoid of FVIII** include major elective surgery, particularly when repeated infusions are foreseen in patients at high risk for thrombosis (old age, cancer surgery, orthopedic surgery), and long-term prophylaxis (target joints, recurrent gastrointestinal bleeding, recurrent epistaxis in children)

In type 3 patients with alloantibodies, all plasma concentrates containing VWF must be avoided because of the risk of anaphylactic reactions. r-FVIII, administered at very high doses by continuous intravenous infusion, or r-FVIIa can be used instead.


**Abbreviations:** VWD, von Willebrand disease; VWF, von Willebrand factor; FVIII, factor VIII; LMWH, low molecular weight heparin; r-FVIII, recombinant factor VIII; RCo, ristocetin cofactor; FVIII:C, factor VIII procoagulant activity.
the aim of achieving FVIII levels always >1–2 U/dL with infusion of 25–40 IU/kg concentrates three times per week on non-consecutive days or every other day. According to different national guidelines and the Italian Association of Haemophilia Centres (AICE, Associazione Italiana Centri Emofilia) recommendations, recombinant FVIII concentrates represent the product of choice in children. The development of IgG alloantibodies (inhibitors) directed against FVIII, neutralizing its activity by a rapid clearance of infused FVIII and resulting in a marked reduction or absence of efficacy, is nowadays the most serious complication of treatment with clotting factor concentrates in HA. Inhibitors make replacement therapy ineffective. As a consequence the patients cannot continue prophylaxis, with an increased risk of mortality, morbidity, and disability. The incidence of inhibitor is around 30% of severe cases and usually the risk is the greatest during the first 10–15 days of exposure. Since replacement treatment starts early in severe hemophilia, the vast majority of inhibitors occur in pediatric patients, quickly reaching this threshold. The inhibitor risk is significantly reduced in patients with severe HA exposed to FVIII for more than 50–150 days. At variance with these figures, the incidence is ~10% only in patients with mild or moderate HA and the risk increases with increasing exposure days so that these patients are mostly adults. The pathogenesis of inhibitors is multifactorial and not fully understood, although several risk factors have been identified. Both genetic factors (ie, F8 mutations, family history of inhibitors, ethnicity, polymorphisms of immune response genes, human leukocyte antigen, and FVIII haplotypes) and environmental factors (ie, age at first FVIII exposure, intensive FVIII treatment, surgery, and prophylaxis) have been implicated. A lower incidence of inhibitors has been recently reported in patients treated with plasma-derived FVIII products compared to those treated with recombinant FVIII, suggesting that the source of FVIII and/or the content of VWF/FVIII concentrates in ITI, in addition to the Inter national Immune Tolerance Study (PRISM) Registry prospectively evaluated the use of VWF/FVIII concentrates in ITI, in addition to the International Immune Tolerance Study. However, in children undergoing ITI for the first time, in keeping with expert recommendations, the same product associated with inhibitor
development should be preferred.66,60,61,77 Alternatively, another recombinant product with similar characteristics could be proposed, using human VW/FVIII concentrates, in children with a previous ITI failure.

Conclusion
The VW/FVIII concentrates play a key role in the management of pediatric patients. They are the treatment of choice for patients with type 3 and type 2B VWD and severe/intermediate patients in whom desmopressin does not work or is contraindicated. Replacement therapy is also required for VWD patients responsive to desmopressin undergoing major surgery and procedures with high bleeding risk, or for those in whom even minor bleeding should be avoided (e.g., neurosurgery). Although recombinant concentrates may represent the treatment of choice in children with HA, the VW/FVIII concentrates may offer an advantage in the success of previously failed ITI with recombinant FVIII.

Disclosure
The authors report no conflicts of interest in this work.

References


