How I treat patients with von Willebrand disease

Pier Mannuccio Mannucci

Von Willebrand disease (vWD) is a frequent inherited disorder of hemostasis that affects both sexes. Two abnormalities are characteristic of the disease, which is caused by a deficiency or a defect in the multimeric glycoprotein called von Willebrand factor: low platelet adhesion to injured blood vessels and defective intrinsic coagulation owing to low plasma levels of factor VIII. There are two main options available for the treatment of spontaneous bleeding episodes and for bleeding prophylaxis: desmopressin and transfusional therapy with plasma products. Desmopressin is the treatment of choice for most patients with type 1 vWD, who account for approximately 70% to 80% of cases. This nontransfusional hemostatic agent raises endogenous factor VIII and von Willebrand factor 3 to 5 times and thereby corrects both the intrinsic coagulation and the primary hemostasis defects. In patients with the more severe type 3 and in most patients with type 2 disease, desmopressin is ineffective or is contraindicated and it is usually necessary to resort to plasma concentrates containing both factor VIII and von Willebrand factor. Concentrates treated with virucidal methods should be preferred to cryoprecipitate because they are equally effective and are perceived as safer.

Introduction

Von Willebrand disease (vWD) is a common inherited bleeding disorder caused by the deficiency or dysfunction of von Willebrand factor (vWF) resulting from mutations in the gene encoding this multimeric glycoprotein. A comprehensive review on vWD and vWF has been recently published. VWF performs two major functions in primary hemostasis and in intrinsic blood coagulation—it mediates the adhesion of platelets at sites of vascular injury, and it stabilizes coagulation factor VIII (VIII) in plasma. In vWD the impairment of these functions is expressed phenotypically by low plasma levels of VIII coagulant activity (VIII:c) and by a prolonged skin bleeding time, at least in the most severe and clinically relevant cases. Bleeding symptoms are usually mild and are characterized by prolonged oozing after minor and major surgery and by mucosal tract hemorrhages such as epistaxis and menorrhagia. Only some of the more severely affected patients have soft-tissue bleeding, such as muscle hematomas and hemarthroses. Childbirth is often a cause of concern, particularly in the postpartum period.

vWD is phenotypically heterogeneous and is classified into three different types (Table 1). Type 1 refers to partial, quantitative deficiency of vWF, and the more severe type 3 refers to complete deficiency. Type 2 vWD refers to qualitative abnormalities of vWF, usually measurable in normal amounts in plasma, and is further subdivided into four subtypes—types 2A, 2B, 2M, and 2N—based on more subtle differences in phenotype (Table 1). Several vWF assays are used in the diagnosis of vWD and its subtypes, such as those that measure the plasma levels of vWF antigen (vWF:Ag), vWF binding to type I or type III collagen (collagen binding activity, vWF:CBA), and vWF interactions with the antibiotic ristocetin and platelet glycoprotein Ib (vWF ristocetin cofactor activity, vWF:RCO). This large number of measurements reflects the fact that none of them is by itself sensitive and specific enough for diagnosis.

Although the treatment of patients with hemophilias A and B is facilitated by the close relation between the content of VIII and factor IX in replacement material, plasma levels attained after infusion, and clinical efficacy, this model cannot be easily translated to the evaluation of products for the treatment of vWD because it is still unclear which VIII or vWF measurement in therapeutic products or in patient plasma better correlates with the severity of clinical bleeding and the efficacy of treatment. The situation is further complicated by the fact that vWD subtypes respond differently to treatment. Two main therapeutic agents are used to stop spontaneous bleeding and to prevent bleeding at the time of surgical procedures: the nontransfusional agent desmopressin and blood products that contain VIII and vWF concentrated from plasma. Additional forms of treatment are platelet concentrates, synthetic fibrinolyis inhibitors, and oral estrogen-progestogen preparations that in some clinical situations are additive or alternative to the two main treatments.

Desmopressin: indications and dosages

Desmopressin (1-deamino-8-D-arginine vasopressin) is a synthetic analogue of the antidiuretic hormone vasopressin that was originally designed for the treatment of diabetes insipidus. When administered to healthy volunteers or patients with mild hemophilia and vWD, desmopressin increases VIII and vWF transiently by releasing these moieties from storage sites into plasma. The mode of action of the compound is only partially understood. Endothelial cell Weibel-Palade bodies appear to be the source of vWF, but the source of VIII has not been determined. Desmopressin induces vWF release into plasma by binding to the vasopressin V2 receptor and thereby activating cyclic adenosine monophosphate-mediated signaling in vascular endothelial cells.
The first clinical trial of desmopressin was successfully performed in 1977; its aim was to avoid the use of blood products in patients with mild hemophilia and vWD who need dental extractions and other surgical procedures. The obvious advantage of this compound is that it is relatively inexpensive and carries no risk for transmitting blood-borne infectious agents. When infused intravenously over 30 minutes at a dose of 0.3 μg/kg diluted in 50 to 100 mL saline, desmopressin is expected to increase plasma VIII and vWF 3 to 5 times above the basal levels within 30 minutes. In general, high VIII–vWF concentrations last in plasma for at least 8 to 10 hours. Because the response in each patient is consistent on different occasions, a test dose of desmopressin administered at the time of diagnosis helps to establish the individual patterns of response. Patients with baseline plasma levels of VIII–vWF measurements in the range of 10 to 20 IU/dL or more are those who are more likely to reach postdesmopressin levels sufficient to attain hemostasis, taking into account variables such as type and severity of the bleeding episode and levels of VIII–vWF that must be maintained to secure hemostasis. Infusions can be repeated every 12 to 24 hours, if necessary. Even though most patients with mild hemophilia A, treated repeatedly with desmopressin, become less responsive to therapy, this problem is less frequent and less prominent in patients with type 1 vWD. The drug is also available in concentrated forms for subcutaneous and intranasal administration (at doses of 0.3 μg/kg and 300 μg, respectively), which can be convenient for home treatment.

Side effects of desmopressin are usually mild tachycardia, headache, and flushing. These symptoms are attributed to the vasodilating effects of the drug and can often be attenuated by slowing the rate of infusion. Hyponatremia and volume overload due to the antidiuretic effect of desmopressin are relative rare if fluid intake is not excessive during treatment. A few cases have been described, mostly in young children who received closely repeated infusions. Even though no episodes of thrombosis have been reported in vWD patients treated with desmopressin, this compound should be used with caution in elderly patients with cardiovascular disease because myocardial infarction and stroke have occurred in a few treated patients with hemophilia and uremia. These thrombotic events are likely to be related to the transient appearance in plasma of ultralarge vWF multimers that originate from the endothelial cells and aggregate platelets directly in conditions of high shear stress, such as those occurring in stenotic arteries. Desmopressin has little or no oxytocic activity and has been used by me without mishap during the early period of pregnancy in 31 women (including carriers of hemophilia A and patients with vWD) with low VIII levels to prevent bleeding at the time of invasive diagnostic procedures, such as chronic villus sampling and amniocentesis (unpublished observations).

Desmopressin is most effective in patients with type 1 vWD, particularly in those who have releasable vWF in storage sites, a condition usually reflected by normal vWF levels in platelets. In these patients VIII, vWF, and bleeding time (BT) are usually corrected to normal values by desmopressin. In other vWD subtypes, responsiveness is varied (Table 2). A poor and short-lasting response is seen in patients with the variant of type 1 vWD that is characterized by low levels of platelet vWF, perhaps because low levels in platelets are paralleled by low levels of releasable vWF in storage sites. In type 2A vWD, VIII levels are usually increased by desmopressin, but the BT is shortened in only a few patients. Desmopressin is contraindicated in type 2B vWD because of the transient appearance of thrombocytopenia. There is little experience in type 2M vWD, but a poor response is predicted because vWF is dysfunctional in this subtype. In type 2N vWD, VIII levels increase after desmopressin, but released VIII circulates for a relatively short time in patients’ plasma because the stabilizing effect of vWF on VIII is impaired by gene mutations affecting the VIII binding site of vWF. Therefore, plasma concentrates containing the VIII and vWF forms are preferable. Patients with type 3 vWD are usually unresponsive to desmopressin because they lack releasable stores of vWF.

### Other nontransfusional therapies for vWD

Two other types of nontransfusional therapy are sometimes used in the management of vWD—synthetic antifibrinolytic amino acids and estrogen–progestogen-containing preparations. Antifibrinolytic amino acids interfere with the lysis of newly formed clots by saturating the binding sites on plasminogen, thereby preventing its attachment to fibrin and making plasminogen unavailable to activation within the forming clot. Epsilon aminocaproic acid (50-60 mg/kg every 4-6 hours) and tranexamic acid (20-25 mg/kg every 8-12 hours) can be administered orally, intravenously, or topically. In the management of the less severe forms of mucosal bleeding, particularly in the nasopharynx, gastrointestinal, and genitourinary tracts, antifibrinolytic amino acids alone may be sufficient to control bleeding. More often they are prescribed as adjutants to replacement therapy with desmopressin and plasma products during minor and major surgery, though few controlled studies have shown the added benefit of this strategy. Estrogens, synthetic or natural, increase plasma vWF levels, but the response is so variable and unpredictable that they are not widely used for therapeutic purposes. It is common clinical experience that the continued use of oral contraceptives containing a synthetic estrogen and a progestogen is useful in reducing the severity of menorrhagia in women with vWD, even in those with severe type 3. VIII and vWF levels are not significantly modified by this treatment; hence, efficacy is thought to be mediated by the changes induced by oral contraceptives on the endometrium that make it less likely to bleed severely at the time of menstruation.

### Table 1. Current classification of von Willebrand disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Partial quantitative deficiency of vWF</td>
</tr>
<tr>
<td>2</td>
<td>Qualitative deficiency of vWF</td>
</tr>
<tr>
<td>2A</td>
<td>Decreased platelet-dependent vWF function, with lack of high molecular weight multimers (HMWM)</td>
</tr>
<tr>
<td>2B</td>
<td>Increased vWF platelet-dependent vWF function, with lack of HMWM</td>
</tr>
<tr>
<td>2M</td>
<td>Decreased platelet-dependent vWF function, with normal multimeric structure</td>
</tr>
<tr>
<td>2N</td>
<td>Decreased vWF affinity for factor VIII</td>
</tr>
<tr>
<td>3</td>
<td>Complete deficiency of vWF</td>
</tr>
</tbody>
</table>

### Table 2. Indications for desmopressin in different types of von Willebrand disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Usually effective</td>
</tr>
<tr>
<td>2A</td>
<td>Usually ineffective</td>
</tr>
<tr>
<td>2B</td>
<td>May be contraindicated</td>
</tr>
<tr>
<td>2M</td>
<td>Predicted to be ineffective</td>
</tr>
<tr>
<td>2N</td>
<td>Rarely effective</td>
</tr>
<tr>
<td>3</td>
<td>Ineffective</td>
</tr>
</tbody>
</table>
Transfusional therapies: indications and dosages

Transfusional therapy with plasma products containing both VIII and vWF is the treatment of choice when bleeding occurs or must be prevented and the predicted response to desmopressin is considered suboptimal for hemostasis. VIII and vWF may be infused as fresh frozen plasma (FFP), but the large volumes required severely limit its use. Cryoprecipitate contains 5 to 10 times more VIII and vWF than FFP (each bag contains approximately 80-100 IU). Early studies indicate that cryoprecipitate administered every 12 to 24 hours normalized plasma VIII levels and stopped or prevented bleeding in vWD. Based on these observations, cryoprecipitate has been the mainstay of treatment for many years. However, virucidal methods cannot be applied to cryoprecipitate as currently produced by blood banks, and this product carries a small but definite risk for transmitting blood-borne infectious agents. Therefore, virus-inactivated VIII–vWF concentrates, originally developed for the treatment of hemophilia A, are perceived as safer and are preferred in the management of patients with vWD unresponsive to desmopressin.

Two commercially available concentrates have been evaluated more extensively than others, and clinical studies have demonstrated their efficacy in preventing or stopping bleeding. One, licensed in the United States and in several European countries for the treatment of vWD, contains relatively larger amounts of VIII:c than of vWF measured as vWF:RCoF (approximately 2-3 times more in terms of IU). The virologic method adopted is pasteurization. The other, licensed only in Europe so far, differs because it contains similar relative amounts of VIII:c and vWF:RCoF. Two virucidal methods, solvent–detergent and heating at high temperature, are included in the manufacturing step with the goal to inactivate both enveloped and nonenveloped virus. Other virally inactivated VIII–vWF concentrates have been successfully used in vWD patients, but clinical experience is more limited. Very high-purity VIII concentrates, obtained by immuno-affinity chromatography on monoclonal antibodies, contain very small amounts of vWF, and the available preparations of recombinant VIII contain none. They are unsuitable for vWD management because the plasma half-life of infused VIII:c is short (1 hour or less) owing to the absence of its carrier vWF both in the actual concentrates and in vWD patients’ plasma. Recently, a chromatography-purified concentrate particularly rich in vWF but with a low VIII content has also been evaluated. This concentrate was clinically efficacious when tested in a small number of patients with type 3 vWD. Efficacy and safety are now under evaluation in Europe in larger series of patients.

The dosages that I recommend for the control or prevention of bleeding are summarized in Table 3. Doses are expressed in IU/kg VIII:c because most of the available concentrates manufactured for the treatment of patients with hemophilia A are labeled in terms of VIII:c content only. Because VIII:c in vWD patients has a longer half-life than it does in patients with hemophilia A (24-26 vs 12-14 hours), the infusion of one daily dose is sufficient to reach and maintain adequate plasma levels for the treatment of spontaneous bleeding episodes and to prevent excessive bleeding until healing is complete, depending on the site and extent of surgery. Because in the United States the Food and Drug Administration is requiring that plasma products licensed for treatment of vWD patients be labeled in terms of the actual defective protein to be replaced, the solvent–detergent, heat-treated concentrate is labeled in terms of vWF:RCoF content. The doses of this concentrate that I recommend for their demonstrated efficacy in a large, prospective clinical trial are 40 to 60 IU/kg (50-75 IU/kg in children because of the lower in vivo recovery), which usually results in vWF:RCoF plasma levels of 80 to 120 U/dL or higher. Even though the plasma half-life of vWF:RCoF is much shorter than that of VIII:c (6-8 vs 24-26 hours), usually these doses do not have to be repeated more often than every 24 hours, but sometimes treatment intervals must be tailored to the clinical situation.

It is usually not necessary to carry out laboratory tests to monitor replacement therapy in patients with spontaneous bleeding episodes. For surgical procedures, I recommend measuring VIII:c every 12 hours on the day of surgery and then every 24 hours. The VIII:c response can be predicted on the basis of pharmacokinetic data, indicating that 1 IU/kg will increase plasma VIII:c levels by approximately 2 U/dL (1.5 U/dL in children). Those who use concentrates labeled in terms of vWF:RCoF content may choose to monitor the plasma levels of this moiety, though it is more complex to measure in the clinical setting and is less standardized than VIII:c levels. It remains to be demonstrated whether newer laboratory measurements, such as the collagen binding assay, will be simpler and more predictive of outcome.

Monitoring the skin bleeding time is usually not necessary. The prolonged bleeding time is frequently not normalized or even shortened in patients treated with VIII–vWF concentrates. There are probably multiple reasons for the inconsistent effects of plasma products on the BT. So far, no concentrate contains a fully functional vWF, as tested in vitro by evaluating the multimeric pattern and using functional assays, because marked vWF proteolysis occurs during purification resulting from the action of platelet and leukocyte proteases contaminating plasma used for fractionation. Despite no or partial correction of the BT, major surgical procedures are successfully carried out and spontaneous bleeding episodes are controlled after the infusion of VIII–vWF concentrates. In the relatively rare instances in which the BT remains prolonged and bleeding is not controlled, platelet concentrates (given immediately after VIII–vWF-containing preparations, at doses of 4.5 × 10¹¹ platelets) are effective, particularly in patients with type 3 vWD, both in terms of BT correction and control of hemorrhages. Platelets from patients with type 3 vWD lack vWF completely, and there is no uptake of the protein from plasma after the infusion of concentrates.

The hemostatic effectiveness of the transfusion of normal platelets likely results because these

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Table 3. Dosages of factor VIII coagulant activity (VIII:c) recommended in patients with von Willebrand disease treated with VIII–vWF concentrates

<table>
<thead>
<tr>
<th>Type of bleeding</th>
<th>Dose (IU/kg)</th>
<th>Number of infusions</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major surgery</td>
<td>40-60</td>
<td>Once a day</td>
<td>Maintain plasma VIII:c &gt; 50 IU/dL until healing is complete, depending on the type of surgery</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>30-50</td>
<td>Once a day or every other day</td>
<td>VIII:c &gt; 30 IU/dL, until healing is complete, depending on the type of surgery</td>
</tr>
<tr>
<td>Dental extractions episodes</td>
<td>20-30</td>
<td>Single</td>
<td>VIII:c &gt; 30 IU/dL for at least 12 hours</td>
</tr>
<tr>
<td>Spontaneous bleeding</td>
<td>20-30</td>
<td>Single</td>
<td>VIII:c &gt; 30 IU/dL</td>
</tr>
</tbody>
</table>

For concentrates labeled in terms of vWF:RCoF, the recommended doses for adults, the number of infusions, and the target plasma levels are the same as those for VIII:c.
cells transport and localize vWF at sites of vascular injury. From a practical standpoint, it must be emphasized that in the largest prospective study carried out thus far in vWD patients, platelet concentrates were necessary to prevent or stop bleeding in one patient only.19

Treatment during pregnancy and delivery

There is no evidence that vWD, even the severe type 3, impairs fertility in affected women or that miscarriages are more frequent in these patients than in women without vWD.35 During normal pregnancy, vWF and VIII levels tend to rise spontaneously in women with types 1 and 2 vWD,36 but this rise does not start until the 10th to 11th week of gestation. Because the degree of rise during pregnancy is variable, patients with type 1 vWD should be monitored with VIII:c assays in the days before parturition and for 1 to 2 weeks afterward—times when plasma levels fall rapidly and late bleeding may occur. In these patients VIII:c levels are the best predictor of the risk for bleeding at parturition and in the postpartum period.36 The risk for bleeding is minimal when VIII:c levels are higher than 40 U/dL, but it can be significant when they are lower than 20 U/dL. In the latter, it may be necessary to administer desmopressin at the time of parturition, particularly with caesarean delivery, and for 2 to 3 days thereafter. Careful surgical hemostasis along with effective uterine contraction usually compensates for a prolonged BT.36 In patients with type 3 vWD, because VIII:c levels are and remain low or unmeasurable throughout pregnancy, monitoring is of little use during pregnancy, but replacement therapy with plasma concentrates and VIII:c monitoring are necessary during and after parturition.35 In my experience, 3 to 4 daily doses of VIII–vWF concentrates (40-60 VIII:c or vWF:RCoF IU/kg) are needed to avoid postpartum bleeding, which often occurs when women with type 3 vWD are not treated at all or are treated for a short period of time.35 During pregnancy, thrombocytopenia may develop or become aggravated in patients with type 2B vWD,37 but it is unclear whether thrombocytopenia exacerbates bleeding.

Treatment of patients with allo-antibodies to von Willebrand factor

Anti-vWF alloantibodies develop after multiple transfusions in 10% to 15% of patients with type 3 vWD.38 The prevalence and natural history of this complication is roughly similar to that occurring in patients with hemophilia A.39,40 In whom the infusion of vWF concentrates not only is ineffective, it may cause postinfusion anaphylactic reactions because of the formation of immune complexes that activate the complement system.41,42 These reactions may be life-threatening.42 There is little experience in the management of these patients with agents other than VIII–vWF concentrates. I was able to successfully treat a patient who had previously had life-endangering anaphylactic reactions and was now undergoing emergency abdominal surgery with recombinant VIII because this product, completely devoid of vWF, was the only one that did not cause the formation of immune complexes and anaphylactic reactions.43 Because of the very short half-life of VIII devoid of its vWF carrier, recombinant VIII had to be administered by continuous intravenous infusion, at very large doses sufficient to maintain VIII:c levels greater than 50 U/dL for 10 days after surgery.43 Even though there is limited clinical experience on the use of recombinant activated factor VII in these patients, there are theoretical reasons to believe that this vWF-free product might provide nonspecific surgical hemostasis bypassing the defect in intrinsic coagulation.

Conclusions

The different options available for the management of von Willebrand disease are summarized in Table 4. Treatment of spontaneous bleeding episodes and their prevention at the time of invasive procedure is relatively simple and can certainly be tackled by the average clinical hematologist with access to a minimum of laboratory testing (factor VIII:c assays). However, the patients must be well characterized phenotypically because the choice of treatment must be tailored to the different types and subtypes of the disease. Such characterization is not simple. In most clinical centers, it is probably not worthy to set up relatively complicated tests such as multimer analysis and vWF:RCoF assay when samples can be sent for analysis to more expert laboratories that have become proficient during the study of large series of patients.

References


<table>
<thead>
<tr>
<th>Type</th>
<th>Treatment of choice</th>
<th>Alternative or adjunctive therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Desmopressin</td>
<td>Antifibrinolytic amino acids</td>
</tr>
<tr>
<td>2A</td>
<td>Factor VIII–vWF</td>
<td>As above</td>
</tr>
<tr>
<td>2B</td>
<td>Factor VIII–vWF</td>
<td>As above</td>
</tr>
<tr>
<td>2M</td>
<td>Factor VIII–vWF</td>
<td>As above</td>
</tr>
<tr>
<td>2N</td>
<td>Factor VIII–vWF</td>
<td>As above</td>
</tr>
<tr>
<td>3</td>
<td>Factor VIII–vWF</td>
<td>As above</td>
</tr>
<tr>
<td>3, complicated by alloantibodies</td>
<td>Recombinant factor VIII</td>
<td>Recombinant activated factor VII</td>
</tr>
</tbody>
</table>

Table 4. Summary of management of different types and subtypes of von Willebrand disease.


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