REVIEW ARTICLE

DRUG THERAPY

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Treatment of von Willebrand's Disease

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Von Willebrand's disease is an inherited bleeding disorder with a prevalence as high as 1 to 2 percent in the general population, according to screening studies.[1,2] In contrast, estimates based on referral for symptoms of bleeding suggest a prevalence of 30 to 100 cases per million, which is similar to the prevalence of hemophilia A.[1,2] The disease was first described in 1926 by the Finnish pediatrician Erik von Willebrand, who used a rowboat to make house calls to patients with the disease in the Åland archipelago. The disease is caused by the quantitative deficiency or dysfunction of von Willebrand factor, a large multimeric glycoprotein[3,4] that is encoded by a gene spanning 178 kb of genomic DNA on chromosome 12.[5,6] The gene product is a 2813-amino-acid polypeptide, consisting of a 22-amino-acid signal peptide and a 741-amino-acid propeptide that is cleaved during intracellular processing, resulting in a mature subunit of 2050 amino acids.[7] Synthesized in vascular endothelial cells and megakaryocytes, stored in Weibel–Palade bodies, and secreted into plasma and the subendothelial extracellular matrix,[7-9] von Willebrand factor has two main functions in hemostasis. It is essential for platelet-plug formation as an adhesion protein that diverts circulating platelets to the sites of vascular injury (Fig. 1), particularly through larger multimers,[7] and it forms a noncovalent complex with coagulation factor VIII in plasma, thereby protecting it from inactivation and clearance (Fig. 2).[10,11]

Even though the primary deficiency or defect in von Willebrand's disease is that of von Willebrand factor, the secondary deficiency of factor VIII, which is dependent on von Willebrand factor as its naturally occurring plasma carrier and stabilizer, leads to a defect both in platelet-plug formation (which occurs in thrombocytopathies such as Glanzmann's thrombasthenia) and in fibrin formation (which occurs in coagulopathies such as the various types of hemophilia). The principal clinical manifestations of von Willebrand's disease reflect this dual defect, with excessive and prolonged bleeding after surgery (which is typical of coagulopathies) and mucosal tract hemorrhages such as epistaxis and menorrhagia (which are typical of thrombocytopathies).[12,13] Only the most severely affected patients have spontaneous soft-tissue bleeding, such as hematomas and hemarthroses, so musculoskeletal abnormalities occur rarely, in contradistinction to hemophilia.[12,13] Excessive bleeding at the time of menstruation and during childbirth is a particular concern for women of childbearing age.[12-14]

CLASSIFICATION

Von Willebrand's disease is classified into three main phenotypes (Table 1).[15] Type 1 (which accounts for 60 to 80 percent of cases) is characterized by mild-to-moderate quantitative deficiencies of von Willebrand factor and factor VIII, which are coordinately reduced to 5 to 30 percent of normal plasma levels (5 to 30 IU per deciliter). This subtype is typically transmitted as an autosomal dominant trait in the heterozygous state.

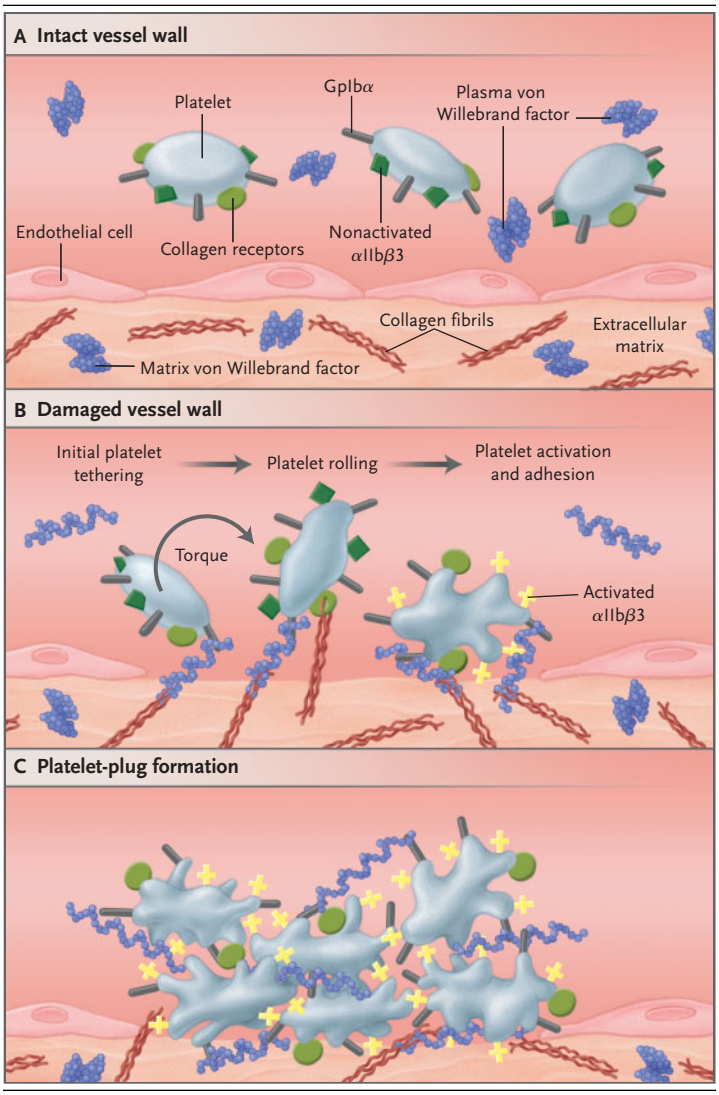

Figure 1. Simplified Model of von Willebrand Factor Functions in Platelet-Plug Formation.

In the intact vessel wall (Panel A), endothelial cells hamper the interactions of circulating platelets and their membrane glycoproteins Ibα (GpIbα), nonactivated IIb–IIIa (αIIbβ3), and collagen receptors GpVI and α2β1 with von Willebrand factor and collagen fibrils localized in the subendothelial extracellular matrix. When the vessel wall is intact and blood flow is normal, plasma von Willebrand factor that is present in a coiled structure and platelets coexist in circulating blood with minimal interactions. In the damaged vessel wall (Panel B), collagen and von Willebrand factor of the subendothelial matrix become exposed to flowing blood and shear forces. Plasma von Willebrand factor efficiently binds to exposed collagen and uncoils its structure, supporting the adhesion of circulating platelets in synergy with collagen. Bound von Willebrand factor interacts, at first, only with the platelet receptor GpIbα and platelet tethering occurs. This interaction has a fast dissociation rate, and platelets tethered to the vessel wall still move in the direction of flow (rolling). In this interaction, collagen receptors GpVI and α2β1 bind to collagen and promote platelet adhesion and activation in synergy with the von Willebrand factor–GpIbα interactions. Once platelets are activated (represented by irregular margins), a conformational change of αIIbβ3 enhances its affinity for the ligand von Willebrand factor (receptors are shown as yellow crosses). This event, together with the rolling of platelets due to the von Willebrand factor–GpIbα interaction, allows αIIbβ3 to bind platelets to the vessel wall (Panel C); αIIbβ3 is also responsible for platelet-to-platelet interactions that eventually lead to platelet-plug formation mediated by von Willebrand factor and, at slow flow conditions, by fibrinogen (not shown).

Type 2 (which accounts for 10 to 30 percent of cases) is characterized by qualitative abnormalities of von Willebrand factor and is further divided into subtypes 2A, 2B, 2M, and 2N. Inheritance is generally autosomal dominant (Table 1). Type 3 (which accounts for 1 to 5 percent of cases) is transmitted as an autosomal recessive trait in homozygous or compound heterozygous persons and is characterized by very low or undetectable levels of von Willebrand factor in plasma (less than 1 percent of normal plasma levels), with low but usually detectable levels of factor VIII (1 to 10 percent of normal plasma levels).[16] It is in these rare cases of type 3 disease (1 in 1 million people) that symptoms are more frequent and severe, similar to those in cases of moderately severe hemophilia A.[13]

At the moment, no genotypic classification of von Willebrand's disease is available. More than 250 mutations of all types (including large and small deletions, out-of-frame insertions, splicing abnormalities, and nonsense and missense mutations) have been identified. More information on the genetic aspects of von Willebrand's disease can be found at www.sheffield.ac.uk/vwf and in a recent review article.[17]

LABORATORY DIAGNOSIS

Normal screening tests of coagulation, such as measuring the activated partial-thromboplastin time and prothrombin time, do not rule out von Willebrand's disease. Before the 1970s, the disease could be diagnosed only on the basis of low plasma levels of factor VIII and a prolonged bleeding time (the bleeding time is normal in hemophilia A).[18] More

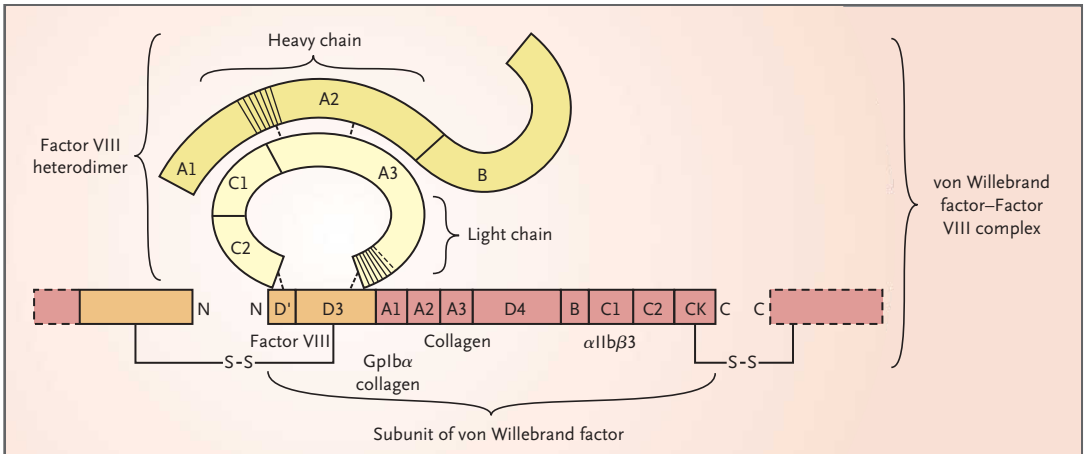

Figure 2. Model of von Willebrand Factor–Factor VIII Complex in Plasma.

Von Willebrand factor circulates as a complex with factor VIII, thereby protecting factor VIII from degradation by the naturally occurring anticoagulant-activated protein C and localizing factor VIII at the site of vascular injury. Each mature von Willebrand factor subunit (domains D', D3, A1, A2, A3, D4, B, C1, C2, CK) dimerizes through disulfide bonds (shown as S–S) near the carboxy terminus (C). Each dimer further multimerizes through disulfide bonds near the amino terminus (N). Factor VIII (domains A1, A2, B, A3, C1, C2) is cleaved before secretion and binds to von Willebrand factor as a heterodimer. The acidic region (cross-hatching) of the A3 domain of factor VIII and the carboxy-terminal region on the C2 domain bind (noncovalent bonds are shown as dotted lines) in the amino-terminal region of the von Willebrand factor subunit (domain D'–D3). The A1 and A2 domains of the heavy chain of factor VIII are noncovalently bonded to the A3 domain of the light chain (dotted lines). At the bottom of the figure, areas of the von Willebrand factor subunit involved in the interaction with collagen and platelet glycoproteins Ibα (GpIbα) and αIIbβ3 are shown.

specific assays for von Willebrand factor were subsequently developed, such as those measuring the immunoreactive protein (von Willebrand factor antigen)[19] and its binding to the platelet membrane glycoprotein Ibα, mediated by the antibiotic ristocetin (ristocetin cofactor activity),[20,21] and to collagen fibrils.[22,23] Other diagnostic methods measure the capacity of von Willebrand factor to bind (and thereby stabilize) factor VIII[24] or evaluate the multimeric pattern of the protein.[25,26] Owing to the limited sensitivity, specificity, and reproducibility of these tests, none of them alone suffices to make a diagnosis. In general, hemostasis laboratories diagnose von Willebrand's disease with four relatively simple tests that measure bleeding time and levels of factor VIII, von Willebrand factor antigen, and ristocetin cofactor activity. Multimeric analysis and the factor VIII binding assay require more specialized expertise but are necessary because distinguishing among the subtypes of the disease has therapeutic implications, as described below.

The limitations of the available assays of von Willebrand factor function should be kept in mind when results are interpreted in the clinical context. For instance, the bleeding time, still largely used for diagnostic purposes because it provides information about platelet-plug formation in vivo, is neither specific for nor sensitive to mild deficiencies of von Willebrand factor. Hence, a normal bleeding time does not exclude the possibility of some types of von Willebrand's disease. In vitro alternatives to this test, such as a test performed with a platelet-function analyzer, have variable sensitivity and specificity.[27,28] Ristocetin cofactor activity and collagen binding activity are artificial surrogates for the platelet-dependent functions of von Willebrand factor and the adhesion of the protein to subendothelial collagen (Fig. 1). The preoperative measurement of von Willebrand factor antigen is of little help in predicting bleeding in patients with type 1 von Willebrand's disease.[29]

GENERAL PRINCIPLES OF TREATMENT

In von Willebrand's disease, as in hemophilia, the mainstay of treatment is the replacement of the deficient protein at the time of spontaneous bleeding or before invasive procedures are performed. Regular prophylaxis is not used as frequently as it is in

Table 1. Phenotypic Classification and Genetic Transmission of von Willebrand's Disease.

Phenotype	Mechanism of Disease	Genetic Transmission
1	Partial quantitative deficiency of von Willebrand factor (and factor VIII)	Autosomal dominant*
2	Qualitative defects of von Willebrand factor	Autosomal dominant†
A	Defective platelet-dependent von Willebrand factor functions, associated with lack of larger multimers	
B	Heightened platelet-dependent von Willebrand factor functions, associated with lack of larger multimers	
M	Defective platelet-dependent von Willebrand factor functions, not associated with multimer defects	
N	Defective von Willebrand factor binding to factor VIII	
3	Severe or complete deficiency of von Willebrand factor and moderately severe factor VIII deficiency	Autosomal recessive

* This mode of transmission is sometimes not evident because of reduced penetrance and varied expressivity.
† Rare cases are characterized by autosomal recessive transmission.

patients with hemophilia A and B, because the bleeding tendency is usually less severe. However, prophylaxis should be contemplated in patients with type 3 disease who have had recurrent hemorrhages in the joints or in the gastrointestinal tract. In hemophilia A and B, the choice of treatment and dosage is based on the close relation among the factor VIII or factor IX content in replacement materials, the corresponding postinfusion plasma levels, and control of bleeding.[30] This equation is only partially relevant in von Willebrand's disease, because it is still uncertain which laboratory measurement best correlates with the severity of bleeding and its control by treatment. Plasma factor VIII is the most important determinant of surgical and soft-tissue bleeding,[31,32] but it is not clear which measurement is the most important determinant of mucosal tract bleeding.[33-35] Little information exists about the levels of ristocetin cofactor activity or collagen binding activity that are critical for the control of mucosal tract or surgical bleeding.

The mainstays of therapy are desmopressin, which induces secretion of autologous factor VIII and von Willebrand factor into plasma, and plasma concentrates, which supply allogeneic forms of these moieties. Fibrinolysis inhibitors, platelet concentrates, and oral estrogen–progestogen preparations are administered as adjuvant treatments.

AUTOLOGOUS REPLACEMENT THERAPY

Desmopressin (1-deamino-8-D-arginine vasopressin) is a synthetic derivative of antidiuretic hormone that acts through type 2 vasopressin receptors and is nearly devoid of activity through type 1 receptors.[36] In normal persons and in patients with mild hemophilia and von Willebrand's disease, desmopressin transiently increases both factor VIII and von Willebrand factor levels.[37] The advantages of using desmopressin as a therapeutic agent are its relatively low cost and unlimited availability and the fact that plasma concentrates can be avoided. The most likely mechanism by which desmopressin increases von Willebrand factor is through cyclic adenosine monophosphate signaling to mediate secretion from Weibel–Palade bodies in endothelial cells into plasma.[38] The site of storage and secretion of factor VIII is unknown.

DOSAGE AND ROUTES OF ADMINISTRATION

Desmopressin, which is administered to children and adults at a dose of 0.3 μg per kilogram of body weight by continuous intravenous infusion for 30 minutes, increases plasma factor VIII and von Willebrand factor levels, on average, by three to five times the baseline levels within 30 to 60 min-

utes.[37,39,40] Intravenous administration is preferred for treatment of acute bleeding episodes and before surgery. Desmopressin is also available in formulations for subcutaneous injection (at a dose of 0.3 μg per kilogram) and nasal inhalation (at a fixed dose of 300 μg in adults and 150 μg in children), routes of administration that are convenient for prophylaxis and for self-treatment at home. Oral administration has not been evaluated for use in von Willebrand's disease.

CLINICAL EFFICACY

Because the response to desmopressin in each patient is generally consistent,[41] a test dose given at the time of diagnosis or before elective treatment is the best way to establish the individual pattern of response and to predict clinical efficacy. The test dose should be given at the doses discussed above, with the route of administration that will be adopted for treatment of bleeding. Factor VIII and ristocetin cofactor activity or collagen binding activity should be measured at least twice after the infusion — at one hour, to obtain information about the patient's peak level, and at four hours, to obtain information about the clearance rate. In practice, patients with any phenotype and plasma levels of factor VIII and von Willebrand factor in the range of 10 to 20 percent of the normal levels or higher before the administration of desmopressin are more likely than those with lower levels to have postinfusion levels that are sufficient to prevent or control bleeding. For instance, plasma levels of factor VIII and von Willebrand factor that are 10 percent of the normal levels are likely to increase to 30 to 50 percent of the normal levels after treatment; those increases may be sufficient for dental extraction, but not for major surgery. On the other hand, plasma factor levels that are 20 percent of the normal levels or more may increase to 60 to 100 percent after the administration of desmopressin, and these levels should be high enough for any surgical procedure. Since the increase in factor levels in plasma lasts for 8 to 10 hours after treatment,[39] desmopressin should be administered every 12 to 24 hours, if necessary. However, tachyphylaxis develops in some patients.[40] In general, treatment with desmopressin can be usefully repeated two to four times, but it is preferable to monitor the factor VIII response and tailor repeated treatments on the basis of the results.

RESPONSE AND PHENOTYPES

Patients with type 1 von Willebrand's disease, who have a functionally normal von Willebrand factor, are more likely to have a response to desmopressin than are patients with type 2 disease, who secrete a qualitatively abnormal moiety.[42-44] Desmopressin is not usually recommended in type 2A von Willebrand's disease because any increase in von Willebrand factor is dysfunctional and hence not effective for primary hemostasis,[44] though there are exceptions.[42] Desmopressin is generally contraindicated in type 2B von Willebrand's disease because of the occurrence of transient thrombocytopenia after administration of the drug.[45] Most patients with type 2M von Willebrand's disease have unsatisfactory laboratory responses to desmopressin,[42,46] but in practice the administration of a test dose is advised to aid in making clinical decisions. In type 2N disease, factor VIII levels increase in response to desmopressin, but in some cases the protein circulates for a short time because gene mutations affecting the factor VIII binding domain blunt the stabilizing effect of von Willebrand factor.[42,47] Therefore, plasma concentrates containing von Willebrand factor that bind factor VIII normally would seem preferable, except when the test dose of desmopressin indicates that peak levels and clearance rates of factor VIII predict adequate hemostasis.[42] With rare exceptions,[48] patients with type 3 von Willebrand's disease do not have a response to desmopressin because they lack releasable stores of von Willebrand factor.[44]

ADVERSE EFFECTS

Adverse effects of desmopressin, including tachycardia, headache, and facial flushing, are common but generally mild. Hyponatremia due to water retention caused by the antidiuretic effect of desmopressin is rare if excessive fluid intake is avoided. However, seizures occasionally occur as a result of water intoxication, making the stringent monitoring of body weight important, particularly in small children who receive repeated treatments.[49] The drug should not be used in patients with unstable coronary artery disease,[50,51] because ultralarge von Willebrand factor multimers that are transiently secreted by endothelial cells into plasma[44] aggregate platelets directly under conditions of high fluid shear stress and may cause myocardial infarction.[52,53]

ALLOGENEIC REPLACEMENT THERAPY

Fresh-frozen plasma contains both factor VIII and von Willebrand factor, but the large amounts that are needed to attain hemostatic concentrations (i.e., 20 to 25 ml per kilogram) may cause volume overload. Eight to 12 bags of cryoprecipitate, which contains both factors at higher concentrations than are found in plasma, normalize plasma factor levels and stop or prevent bleeding.[54] However, methods for virus inactivation are not routinely applicable to this plasma fraction. Hence, virus-inactivated plasma concentrates that contain both factor VIII and von Willebrand factor are considered to be safer and are preferable for patients who are not candidates for desmopressin treatment.

REPLACEMENT PRODUCTS

Humate-P, one of the two commercial concentrates of antihemophilic factor that have been evaluated extensively in clinical studies, contains larger amounts of von Willebrand factor than it does factor VIII (by a factor of approximately two to three).[55-58] The concentrate is pasteurized to inactivate blood-borne viruses. The other concentrate, Alphanate, contains similar relative amounts of factor VIII and ristocetin cofactor activity of von Willebrand factor[59]; solvents and detergents, as well as heating at a high temperature, are used for virus inactivation. A few studies indicate that other commercial concentrates that contain both factors are also clinically efficacious, but the available data are limited and retrospective.[60-63] Products containing highly purified factor VIII that are obtained by recombinant DNA techniques or from plasma should not be used because they lack von Willebrand factor, and the infused factor VIII therefore has a very short half-life.[64] A plasma concentrate that contains highly purified von Willebrand factor with very little factor VIII (Wilfactin) has been clinically evaluated in type 3 and other types of von Willebrand's disease.[65,66] The rationale for its use is that patients with von Willebrand's disease have an intact endogenous production of factor VIII, provided the deficiency of its stabilizer is corrected by infusion of von Willebrand factor. The postinfusion levels of factor VIII rise slowly and peak between six and eight hours; therefore, in patients with baseline factor VIII levels that are 20 to 30 percent or less of normal levels, coadministration of a priming dose of factor VIII (for instance, a recombinant or monoclonal product) is necessary if hemostasis must be achieved promptly because of acute bleeding or emergency surgery.[66] Patients who undergo elective surgery should receive a concentrate infusion six to eight hours before the procedure in order to allow enough time for new synthesis of endogenous factor VIII. With the exception of plasma and cryoprecipitate, all plasma concentrates used for treatment so far lack the largest von Willebrand factor multimers,[67,68] but there is no evidence that their absence adversely affects the outcome of treatment.[59]

DOSAGE OF CONCENTRATE

The average dosages of concentrates recommended for the control or prevention of different types of hemorrhages are shown in Table 2. Since only a few prospective studies have gauged the effectiveness of the dosages,[57-59] the level of evidence supporting these recommendations is relatively low. Dosages in Table 2 are expressed in international units per kilogram of body weight for factor VIII coagulant activity, because most concentrates are labeled solely in terms of this moiety. The dosages are indicated for patients with severe deficiencies of both factor VIII and von Willebrand factor (levels that are approximately 10 percent or less of normal levels) and must be proportionally reduced in patients with less severe deficiencies in order to attain the same target levels of the factors. It is now frequently required that concentrates licensed for treatment of von Willebrand's disease be labeled with the potency of both ristocetin cofactor and factor VIII.[69] The recommended dosages of ristocetin cofactor are similar to those of factor VIII,[57-59] because the in vivo recovery of the two moieties is similar (i.e., approximately a 2 percent increase in plasma for each international unit per kilogram administered).

LABORATORY MONITORING

When a patient undergoes surgery or receives repeated therapeutic doses of concentrates, factor VIII activity should be assayed every 12 hours on the day a dose is administered and every 24 hours thereafter. This is necessary not only because factor VIII is the main predictor of surgical hemostasis[31,32,35] but also to avoid reaching supranormal levels (i.e., 200 percent or more), which may increase the risk of venous thromboembolism (Fig. 3).[70,71] Treat-

Table 2. Average Recommended Dosages of Factor VIII (Coagulant Activity) and von Willebrand Factor (Ristocetin Cofactor Activity) for Patients with Phenotypes of von Willebrand's Disease Associated with Severely Reduced Factor Levels (10 Percent or Less of Normal Levels).

Type of Hemorrhage	Dose (IU/kg)*	Frequency of Infusions	Target
Major surgery	50	Daily	Trough factor VIII level >50% of normal level until healing is complete (usually, 5–10 days)
Minor surgery	40	Daily or every other day	Trough factor VIII level >30% of normal level until healing is complete (usually, 2–4 days)
Dental extraction	30	Single dose	Factor VIII level >50% of normal level for 12 hr
Spontaneous bleeding episode	25	Daily	Factor VIII level >30% of normal level until bleeding stops (usually, 2–4 days)
Delivery and puerperium	40	Daily before delivery and in the postpartum period	Factor VIII level >50% of normal level for 3–4 days

* In children, all doses should be increased by 20 percent to account for the greater plasma volume. (For instance, instead of receiving a dose of 40 to 50 IU per kilogram, a child would receive 48 to 60 IU per kilogram.)

ment may also be monitored with ristocetin cofactor as a measure of von Willebrand factor activity.[69] The peak and trough plasma levels of ristocetin cofactor that are needed to achieve and maintain surgical hemostasis are similar to those of factor VIII.[57-59] However, monitoring ristocetin cofactor alone may be inappropriate during prolonged treatment, because plasma levels of this moiety fall rapidly, with a half-life of 8 to 10 hours,[55,59] while factor VIII continues to rise to unnecessarily high levels as a result of endogenous factor VIII production (with a half-life of 24 to 26 hours, instead of 10 to 14 hours as in hemophilia A [Fig. 3]). Measuring the bleeding time is not necessary in the postoperative period. This test is often not normalized or even shortened in patients who are treated with cryoprecipitate[72] or concentrates.[68] Despite this fact, hemorrhage that is associated with surgical procedures and soft-tissue bleeding can be controlled successfully[31,32,55-59] if factor VIII levels are maintained at recommended levels (Table 2).

When hemorrhage is not controlled despite adequate factor VIII levels, platelet concentrates given together with plasma products, at doses of 4×10^{11} to 5×10^{11} platelets, often control bleeding.[73-76] Transfused normal platelets are thought to be hemostatically effective because they transport and localize von Willebrand factor from the rapidly flowing blood into the sites of vascular injury.[73,75]

Table 3 summarizes the options that are currently available for replacement therapy for the various phenotypes of von Willebrand's disease.

ANTIFIBRINOLYTIC AMINO ACIDS

The manifestations of bleeding that are most frequently seen in von Willebrand's disease — such as epistaxis and menorrhagia — are sustained, in part, by the rich fibrinolytic activity of mucosal tracts. Local fibrinolytic activity in the buccal mucosa and gums also compromises hemostasis during dental extractions. These findings are the basis for the therapeutic use of antifibrinolytic amino acids in von Willebrand's disease, as well as in other inherited bleeding disorders.[77] Aminocaproic acid (at a dose of 50 to 60 mg per kilogram every 4 to 6 hours) or tranexamic acid (at a dose of 10 to 15 mg per kilogram every 8 to 12 hours) can be administered orally, intravenously, or topically.[77] Antifibrinolytic amino acids may be sufficient in the management of the less severe forms of mucosal bleeding. More often these agents are prescribed as adjuncts to replacement therapy with desmopressin and plasma concentrates during both minor and major surgery. Antifibrinolytic amino acids are associated with rare adverse effects such as nausea and diarrhea. They are contraindicated in patients with gross hematuria because clots that do not lyse may cause ureteral obstruction.

REPRODUCTIVE HEALTH

Von Willebrand's disease does not impair fertility, and miscarriages do not occur with increased frequency.[13,14] However, the disease has a negative effect on women's health and quality of life mainly because of menorrhagia and excessive bleeding at parturition.

MENORRHAGIA

Among 271 women with no pelvic disease who had objectively documented excessive blood loss at menstruation, 7 to 13 percent had low von Willebrand factor levels.[78] Conversely, menorrhagia is a frequent symptom in women with von Willebrand's disease.[79,80] For instance, in one study, 69 of 130 women with type 3 disease who were of childbearing age[13] had menstrual blood losses that were sufficient to cause iron-deficiency anemia. In women with type 3 disease, oral estrogen–progestogen preparations have a success rate as high as 88 percent in reducing blood loss,[14] probably because these drugs render the endometrium less susceptible to bleeding. Intranasal or subcutaneous administration of desmopressin,[81,82] antifibrinolytic amino acids, or both has also been proposed, but there is insufficient evidence of their efficacy, safety, and acceptability. Unlike type 1 vasopressin agonists, desmopressin has little or no oxytocic activity, so it can be used in pregnant women (those who are carriers of hemophilia A or who have type 1 von Willebrand's disease) before surgery or invasive diagnostic procedures, such as chorionic villus sampling and amniocentesis, are performed.

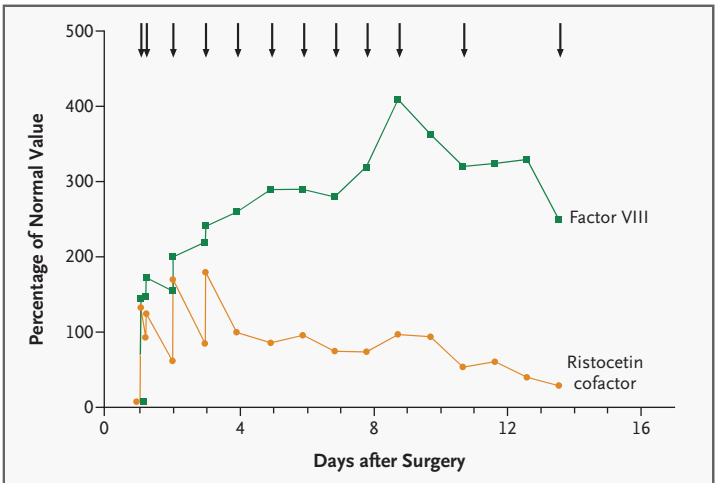

Figure 3. Representative Example of the Changes of Plasma Levels in Ristocetin Cofactor Activity and Factor VIII Coagulant Activity in a Patient with Type 3 von Willebrand's Disease.

Ristocetin cofactor activity and factor VIII coagulant activity are shown in a patient who had undergone elective hip replacement and who was treated repeatedly with a plasma concentrate containing factor VIII and von Willebrand factor, with doses determined on the basis of ristocetin cofactor activity. The black arrows show the times of administration of the concentrate. In an attempt to keep ristocetin cofactor activity close to 100 percent in the early postoperative period (up to day 9), 50 IU per kilogram of body weight of this moiety was given at approximately daily intervals. The target levels of ristocetin cofactor activity were achieved, but factor VIII levels increased progressively to more than 400 percent of the normal value. On postoperative day 12, a nonfatal pulmonary embolism developed in the patient, who had received no antithrombotic prophylaxis. Low-molecular-weight heparin should be given prophylactically to patients who are undergoing surgery, with the use of the same doses and schedules that are recommended for patients without von Willebrand's disease who are undergoing similar procedures.

MANAGEMENT OF DELIVERY

During and after delivery, measures aimed at rapid and complete contraction of the uterus are of utmost importance to prevent excessive bleeding. In women with type 1 disease, factor VIII and von Willebrand factor levels tend to rise spontaneously throughout pregnancy,[83] and often reach normal levels at term. Since factor VIII levels are the best predictor of bleeding during and after delivery,[84-87] they should be measured at term and for two weeks thereafter, when the factor VIII levels fall rapidly and bleeding may occur. The risk of bleeding after vaginal or cesarean delivery is minimal when plasma factor VIII levels are at least 30 to 40 percent of normal levels, but the risk may become clinically significant when they are lower.[84-87] In these instances, it is necessary to administer desmopressin or concentrates at the time of delivery and for three to four days thereafter. Monitoring of the plasma factor VIII levels is of little use during pregnancy or delivery in women with type 3 disease, because the levels remain low. Daily doses of concentrates during and after delivery are needed to prevent bleeding (Table 2).[13,14]

ALLOANTIBODIES

Alloantibodies that inactivate von Willebrand factor and form circulating immune complexes[88] develop in 10 to 15 percent of patients with type 3 disease who have received multiple transfusions, particularly in carriers of large gene deletions.[89] Concentrates that contain von Willebrand factor are contraindicated after this complication has occurred since they elicit life-threatening anaphylactic reactions be-

cause of complement activation by immune complexes.[90,91] There is limited but favorable experience with the use of recombinant factor VIII, which is completely devoid of von Willebrand factor and therefore does not cause the formation of immune complexes.[91,92] Since the plasma half-life of factor VIII in the absence of its carrier is very short (one to two hours) in patients with alloantibodies,[35,91] recombinant factor VIII must be administered by continuous intravenous infusion at very large doses, with the goal of maintaining plasma factor VIII at hemostatic levels until bleeding stops (Table 2).[91,92] There is favorable experience with the use of recombinant activated factor VII. Studies have shown that bolus doses of 90 μg per kilogram given every two hours or 20 μg per kilogram given every hour by continuous intravenous infusion provide surgical hemostasis.[93,94]

ACQUIRED VON WILLEBRAND SYNDROME

An acquired syndrome that resembles von Willebrand's disease in its clinical manifestations and laboratory patterns occurs in rare instances in association with clinical conditions such as lymphoproliferative and autoimmune diseases, essential thrombocythemia, cancer, and valvular heart disease (particularly aortic stenosis).[95] The prevailing mechanisms are accelerated clearance of von Willebrand factor from plasma because of its absorption on the surface of abnormal cells, formation of complexes with other plasma proteins, heightened in vivo proteolysis, and inactivating autoantibodies.[95] The most successful form of treatment is the removal of the underlying cause of the condition, which usually leads to a resolution of the syndrome — for example, valve replacement in aortic stenosis.[96,97] Other options for therapy are the administration of desmopressin, factor concentrates, and intravenous immune globulin.[98] The choice among these options is often determined by the increase in plasma factor levels after the administration of test doses.

THE FUTURE

A recombinant preparation of von Willebrand factor with an intact multimeric structure and adequate post-translational modifications corrects the plasma defects in dogs with von Willebrand's disease.[99,100] The cytokine interleukin-11 increases plasma levels of factor VIII and von Willebrand factor in mice[101] and in humans.[102] In dogs with von Willebrand's disease, interleukin-11 leads to a gradual and sustained rise in factor VIII and von Wille-

Table 3. Summary of Recommended Treatment According to the Phenotypes of von Willebrand's Disease.

Type	Treatment of Choice*	Alternative Therapy
1	Desmopressin†	Factor VIII–von Willebrand factor concentrates
2A	Factor VIII–von Willebrand factor concentrates	Desmopressin
2B	Factor VIII–von Willebrand factor concentrates	None
2M	Factor VIII–von Willebrand factor concentrates	Desmopressin
2N	Factor VIII–von Willebrand factor concentrates	Desmopressin
3		
In patients without alloantibodies	Factor VIII–von Willebrand factor concentrates	Platelet concentrates
In patients with alloantibodies	Recombinant factor VIII	Recombinant activated factor VII

* Adjuvant therapy with antifibrinolytic amino acids is recommended together with first-choice or alternative therapies in all types of von Willebrand's disease. The recommended oral or intravenous dosage of aminocaproic acid is 50 to 60 mg per kilogram of body weight every 4 to 6 hours; the recommended dose of tranexamic acid is 10 to 15 mg per kilogram every 8 to 12 hours.

† Indications for desmopressin cannot be assumed unless a test infusion has shown that factor VIII and von Willebrand factor levels rise adequately for that given bleeding episode or hemostatic challenge.

brand factor levels, which is distinct from the rapid and short-lasting rise observed after the administration of desmopressin.[103] If the cytokine appears to be effective and safe in clinical trials, it may provide a new form of treatment that would complement desmopressin, with the choice of the latter when a short-term hemostatic effect is needed and of interleukin-11 when a sustained effect is needed.

Although gene therapy is being evaluated for hemophilia A and B in phase I clinical studies,[30] this approach is less attractive as a treatment for von Willebrand's disease. Although von Willebrand's disease occurs as frequently as hemophilia, it is usually not as severe, and adequate therapeutic options are available. In addition, the huge size of the complementary DNA makes it difficult to insert it into currently available viral vectors, and massive overexpression of the normal allele is required in the more frequent dominant forms of the disease (type 1, type 2A, and type 2B).

CONCLUSIONS

In the past 15 to 20 years, there have been major advances in our understanding of the pathophysiology, molecular basis, and management of von Willebrand's disease. The main options that are available for treatment (desmopressin and plasma concentrates) are effective in controlling bleeding in most patients with the disease. Even though virus-inactivated products appear to have an acceptable level of safety, it is hoped that the von Willebrand factor that is produced by recombinant DNA techniques will soon undergo clinical trials and become available for replacement therapy.

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