

# ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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## Preventing Excessive Bleeding in Patients With von Willebrand Disease

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**H&O** What are the strategies for preventing excessive bleeding in patients with type 1 von Willebrand disease?

**JG** Type 1 von Willebrand disease (vWD), the more mild form of this disorder, comprises 85–90% of all vWD patients. In this subtype, the von Willebrand factor (vWf) molecule is normal, but patients have a decreased amount of protein in their plasma. There are two strategies employed for increasing the amount of vWf in the circulation for the treatment or prevention of bleeding. One strategy is to increase the patient's own endogenous vWf by administering desmopressin, a vasopressin analog that causes the release of vWf from its storage sites. The second strategy is replacement therapy by transfusion of normal vWf.

The response to desmopressin varies, and therefore it is recommended that patients undergo a trial dose with measurement of responses before it is used for procedures. The response from the trial dose enable one to predetermine whether or not a patient can achieve hemostatic levels of vWf with desmopressin treatment, since individual patients will have a similar response with each administration of desmopressin.

Adjunctive therapy with antifibrinolytic agents such as epsilon-aminocaproic acid (Amicar, Xenodyne) or tranexamic acid (Cyklokapron, Pfizer) is very useful for treatment of all types of vWD for oral bleeding or procedures in the oral cavity.

**H&O** When prophylaxis is needed, is there enough time to conduct this testing?

**JG** When a patient is scheduled for elective procedures, there is usually enough time to test the vWf response to desmopressin. The height of the response will assist in the determination of the type of procedures that may be undertaken with desmopressin treatment in a patient with vWD. If a patient responds to desmopressin with attainment of at least 100% vWf, then it is likely he or she can undergo even major surgery using desmopressin alone. If the response is less than 100% but greater than 50%, major surgery would not be possible with desmopressin alone, but a tooth extraction, for example, would be acceptable. If a patient does not achieve vWf levels of at least 100% following desmopressin administration and requires major surgery, then the patient should be treated with replacement therapy with a product containing normal vWf.

**H&O** Are there situations in which desmopressin is contraindicated for patients with type 1 vWD?

**JG** In general, patients with an increased risk for thrombosis, such as older individuals with atherosclerotic cardiac disease, should not be treated with desmopressin. Thrombotic complications are fairly rare, but they do occur.

Seizures following desmopressin administration have been reported. Most often, this complication is due to failure to adequately restrict fluids. Since desmopressin is a vasopressin analog, it has an antidiuretic effect via its action on the kidneys. If patients are given large amounts of fluid after receiving desmopressin, hyponatremia and seizures may occur. Some patients appear to be more susceptible to this side effect than others. Therefore, a patient with a history of seizure in association with desmopressin therapy should probably not be re-exposed to the drug.

**H&O** What is the second approach for bleeding prophylaxis in type 1 patients?

**JG** The second approach to treat and prevent bleeding is replacement therapy with exogenous vWf. This is currently achieved with plasma-derived products that contain vWf and factor VIII (fVIII). At the present time,

there is only one licensed product in the United States (Humate-P, ZLB-Behring) for use in vWD. Additional concentrates are available in other areas of the world and several are undergoing clinical trials with a goal of licensure by the US Food and Drug Administration for a vWD indication in the United States. Cryoprecipitate is no longer indicated for treatment of vWD because it is not viral-inactivated; however, cryoprecipitate is effective in achieving hemostasis and can be used in emergent situations when the safer, viral inactivated vWf/FVIII concentrates are not available.

A desirable therapeutic option for use in vWD is a recombinant vWf concentrate. There are recombinant FVIII and FIX concentrates for hemophilia A and B, but not for vWD. Such a product would be very beneficial and desirable for patients with vWD who require replacement therapy.

### **H&O** Could a recombinant vWF be developed?

**JG** A recombinant molecule has been expressed in the laboratory and has been infused into a canine vWD model. However, vWf is a very complex molecule, increasing the difficulty of development of a recombinant product for human use. In addition, the number of patients with vWD who require replacement therapy is relatively low, and this will likely limit the interest of pharmaceutical companies in developing such a product.

### **H&O** Because type 2 includes several varieties of patients, let's discuss type 3 vWD first. What is the approach for bleeding prophylaxis for this patient subgroup?

**JG** Type 3 patients have undetectable vWf, and as a result also have low FVIII levels because vWf serves as a stabilizing carrier for FVIII in the circulation. If a patient does not have normal levels of vWf, FVIII is unstable and cleared rapidly from the circulation.

These two manifestations of type 3 vWD—absent vWf and low FVIII—must be taken into consideration when planning therapy. Desmopressin is not effective because there is no vWf to be released from the storage sites. Therefore, replacement therapy with a concentrate that contains both vWf and FVIII must be used to treat these patients.

Treatment and prevention of bleeding in type 3 patients is more complex than treatment of type 1 patients, who frequently have normal or near-normal FVIII levels. The various concentrates that contain vWf and FVIII contain varying vWf:FVIII ratios. In order to calculate the amount of product to administer, the concentrations of both factors must be taken into account.

### **H&O** Is bleeding prophylaxis more important for type 3 patients?

**JG** The answer to this question depends on the situation requiring prophylaxis. In the case of major surgery, the need for replacement therapy in order to prevent bleeding is unquestionable for all types of vWD. However, type 3 vWD patients are more likely to require prophylaxis for target joint bleeding than other types. vWf/FVIII concentrate may be given two to three times per week in order to prevent repeated joint bleeding and the development of chronic joint disease. In addition to type 3 patients, occasional type 2 patients may require prophylaxis for treatment of frequent, severe epistaxis. Individuals with vWD and recurrent gastrointestinal hemorrhage that cannot be treated surgically are also candidates for prophylaxis.

Females with vWD of all types often experience significant menorrhagia. Most can be treated with oral contraceptives. For those who cannot or do not wish to use oral contraceptives, desmopressin is often successful for type 1 and 2 vWD patients and antifibrinolytic therapy with epsilon-aminocaproic acid or tranexamic acid may be effective in all types. However, rarely, particularly in type 3 patients, prophylaxis with a vWf/FVIII concentrate is needed to reduce the menorrhagia.

### **H&O** What considerations are involved in bleeding prophylaxis for type 2 patients?

**JG** Bleeding prophylaxis for type 2 vWD involves some of the same issues as type 3 vWD. The major difference is that some subtypes of type 2 disease can be treated with desmopressin for mild bleeding or minor surgical procedures, such as tooth extractions. There are four subgroups of type 2 vWD—2A, 2B, 2M, and 2N—and each subtype is classified by unique pathophysiologic abnormalities; each, therefore, has different treatment indications for prophylaxis of bleeding or surgery.

### **H&O** How is type 2A disease treated?

**JG** vWf is a complex molecule composed of repeated subunits; the largest molecules are as high as 20 million Daltons. The large molecules composed of multiple subunits are required for normal hemostasis. Patients with type 2A vWD either have a defective molecule that is cleaved into smaller fragments as it is released into the circulation or fail to synthesize the large multimers of vWf.

Patients with the subtype of type 2A vWD that is rapidly cleaved (type 2A2) may have a transient response to desmopressin with improvement in hemostasis until the molecules are cleaved by ADAMTS13 as they enter the circulation. As recommended for type 1 patients, desmopressin responses should be determined in advance.

For patients who cannot synthesize the high-molecular weight multimers at all (type 2A1), there may be no response to desmopressin.

In general, prophylaxis for type 2A patients scheduled to undergo major surgical procedures requires replacement therapy. Some type 2A2 patients may be treated with desmopressin for minor procedures such as a tooth extraction; for oral cavity procedures, use of antifibrinolytic agent for adjunctive therapy may circumvent the need for repeated dosing of desmopressin or for vWf/FVIII therapy.

### **H&O** What are the characteristics of type 2B vWD and how is bleeding prevented in this subgroup?

**JG** In type 2B disease, vWf is more tightly bound to the platelets, resulting in adsorption of high molecular weight multimers onto the platelet surface; this results in clearance of both the high-molecular weight multimers of vWf and platelets. Thus, these patients have thrombocytopenia in addition to vWf abnormalities. Desmopressin raises the level of abnormal molecules and can lead to increased clearance of platelets, and therefore its use in this patient subgroup is controversial. In general, however, desmopressin is not used in this subgroup of patients, though it may be employed in selected minor situations. Most patients with type 2B vWD require replacement therapy for the treatment of bleeding episodes and prior to surgical procedures. Patients with significant thrombocytopenia may also require platelet transfusions.

### **H&O** How is type 2M vWD treated?

**JG** The “M” in the name of this subgroup stands for multimers, which are formed normally in these patients. However, the mutation in type 2M vWD results in decreased binding of vWf to the GP1B vWf platelet receptor. Some patients have a transient response to desmopressin, but as with other subgroups, the response should be measured in advance to determine if vWf activity levels are high enough to promote satisfactory hemostasis.

### **H&O** What are the bleeding prophylaxis requirements for type 2N?

**JG** In type 2N vWD, named for Normandy, the location of the first reported patients, a molecular defect prevents the binding of fVIII to the vWf molecules. Therefore, these patients have low fVIII levels, similar to the levels associated with mild hemophilia. However, in contrast to hemophilia, patients with this vWD subtype require replacement therapy with normal vWf; fVIII concentrates are not effective because fVIII not complexed to vWf is cleared as rapidly as the patient's own fVIII. Some patients in this group have a transient response to desmopressin.

### **Suggested Reading**

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