

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Update on the Management of von Willebrand Disease

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H&O What are the best diagnostic methods in use today in the setting of von Willebrand disease?

ABF During my chairmanship (2003–2006) of the von Willebrand subcommittee of the Scientific Standardization Committees of the International Society on Thrombosis and Hemostasis (SSC-ISTH), one of my major interests was to set up a diagnostic repertoire for von Willebrand disease (VWD). First, it is not possible to compare the diagnostic approach of VWD with that of other heritable bleeding disorders, including hemophilia. In fact, diagnosis of VWD should always be contingent on more than one assay because von Willebrand factor (VWF) deficiency must be investigated according to its multiple domains and their functions. VWF is an adhesive glycoprotein that interacts with platelets and subendothelial matrices (collagen) and therefore it plays a major role in the first phases of hemostasis. VWF is also the carrier of factor VIII (FVIII) and therefore it plays an important role also in blood coagulation. The first interaction of circulating VWF is with its platelet receptor, the glycoprotein Ib (GP1b) alpha. The VWF-GPIb interactions in vivo are induced by blood flow, whereas in vitro interactions between platelet GPIb and plasma VWF can be induced by the antibiotic ristocetin (inducer). Therefore, ristocetin cofactor activity (VWF:RCo), in use for over 30 years, is still the best surrogate marker in the laboratory to assess this important activity of VWF. There are, however, drawbacks to this method. VWF:RCo, usually measured using formalin-fixed platelets in the aggregometer, is specific but not very sensitive when a patient has very low levels of VWF (<15 U/dL). Also, there can be a large coefficient of variation (10–15%) in the VWF:RCo assay.

The VWF collagen binding assay (VWF:CB) has been proposed as an alternative to VWF:RCo. VWF:CB is an enzyme-linked immunosorbent assay (ELISA), allowing the same sensitivity as VWF antigen by ELISA. It is possible to measure low levels (1 U/dL) of VWF with this assay, whereas clinicians should not rely on values below 10 U/dL using standard assays of VWF:RCo activity. However, with VWF:CB there are discrepancies related to the type of collagen (types I, III, or VI) used. Also, animal-derived and human placenta-derived collagens confer different results, and therefore VWF:CB still needs standardization. Moreover, in VWD types 1 and 2, VWF:CB can be normal or abnormal when VWF:RCo levels are reduced; on the other hand, no “bleeder” VWD patients have been found up until now to exhibit abnormal VWF:CB in the presence of normal levels of VWF:RCo. In other words, there is no evidence that VWF:CB can be used instead of VWF:RCo to diagnose VWD but VWF:CB can help to distinguish VWD types 2A, 2B, and 2M when it is used together with VWF:RCo. The next tasks of the subcommittee of the SSC-ISTH will be to improve the potency and standardization of VWF:RCo using the GP1b (recombinant or plasma-derived) in the ELISA. Using this ELISA technique, the sensitivity of VWF:RCo is very high. In summary, I believe VWD diagnosis will be improved by better screening of VWF:RCo with a more sensitive and reproducible assay.

H&O What are the goals of treatment of VWD?

ABF The goal of treatment is to correct the dual defects of hemostasis—ie, abnormal platelet adhesion due to low or defective VWF and abnormal intrinsic coagulation due to low FVIII. Two main therapeutic approaches are available: desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP), which releases endogenous VWF from endothelial cells, and exogenous VWF contained in VWF plasma-derived concentrates. Treatment should be adjusted according to the best diagnostic available; disease management will be efficacious only if diagnosis is done properly. DDAVP is a synthetic analog of vasopressin that is relatively inexpensive and carries no risk of transmitting blood-borne infectious agents. DDAVP, infused intravenously at a dose of 0.3 µg/kg diluted in 50 mL saline over 30 minutes, usually increases plasma VWF and FVIII 3–5 times above baseline levels within 30–60 min-

utes, and, in general, high VWF and FVIII levels last for 6–8 hours. DDAVP is the treatment of choice for VWD type 1 because it can induce release of normal VWF from cellular compartments, and the drug can be clinically useful also in other types of VWD, including acquired von Willebrand syndrome. A test dose of DDAVP at the time of diagnosis is recommended to establish the individual patterns of biologic response and to predict clinical efficacy during bleeding and surgery. DDAVP is not effective in VWD type 3 and in severe cases of VWD 1 and 2, and it can induce transient thrombocytopenia in patients with VWD type 2B. The results of several retrospective studies on the use of DDAVP in the management of VWD have been reported by many authors over the last 30 years. However, despite the widespread use of DDAVP in the treatment of VWD, there are only a few prospective clinical trials in large numbers of cases on the efficacy and safety of DDAVP aimed at determining benefits and limits of this therapeutic approach. An investigator-driven observational prospective study on clinical efficacy of DDAVP in 200 patients with VWD types 1 and 2 has been recently organized: the efficacy and safety of DDAVP will be evaluated prospectively for 24 months during bleeding episodes and minor or major surgeries in VWD patients infused with DDAVP at enrollment.

H&O How is exogenous VWF used in the treatment of VWD?

ABF A second option for treatment is exogenous VWF. VWF/FVIII concentrates are indicated in VWD type 3, in type 2B because DDAVP can induce transient thrombocytopenia, and in all type 1 and 2 patients who are not responsive to DDAVP or who may have contraindications to its use. Minimal requirements for plasma-derived VWF/FVIII concentrates in VWD management are the following: they must contain VWF and some FVIII; they should be utilized via virucidal methods; and they should be tested for pharmacokinetics (PK) and efficacy in retrospective and prospective clinical trials of relatively large numbers of VWD patients. Among several VWF concentrates, only five have been extensively evaluated in PK trials as well as in retrospective or prospective efficacy studies in VWD. The Alphanate Study Group published PK and clinical efficacy results in 2002. This study was the first to enroll not only type 3 (n=12) but also type 2A (n=5) and type 1 (n=18) VWD patients. An important finding in this study was that, in VWD type 3, the half-life of FVIII:C was twice that of VWF antigen (VWF:Ag) due to the endogenous FVIII:C. Efficacy results showed that 75% of bleeding episodes were controlled with one or two infusions, and 71% of patients who received prophylactic treatment for surgeries or invasive procedures had good clinical responses.

In another retrospective study, 22 VWD patients in Italy received Fanhdi, a concentrate similar to Alphan-

ate. Excellent-good clinical responses were seen in 92% of bleeding episodes and in 93% of surgical procedures, despite the relative loss of high-molecular weight VWF multimers in the product. Haemate P/Humate-P, an intermediate-purity VWF/FVIII concentrate, has been widely used in VWD and has been considered the gold standard in management of this disorder. This product was introduced into clinical practice in Europe (Haemate P) in 1984 and in the United States (Humate-P) in 1999. The first PK study of Haemate P, published in 1998, was a single-center evaluation involving 6 type 3 VWD patients. Clinical efficacy data were collected retrospectively and showed excellent-good responses for 99% of surgeries (n=73) and for 97% of bleeding episodes (n=3,440). Results of a large retrospective study organized by the Canadian Hemophilia Centers were published in 2002. Other published studies include a retrospective analysis of Haemate P/Humate-P efficacy and safety in preventing bleeding during surgery or invasive procedures in 26 Italian VWD patients, as well as two prospective, multicenter, open-label, nonrandomized studies conducted in the United States on Haemate P/Humate-P used in urgent bleeding and urgent surgical events.

Another plasma-derived VWF concentrate with low FVIII:C levels was introduced in France in 1992, and the first PK study in VWD type 3 was published in 1996. An improved version of this concentrate, which is almost devoid of FVIII:C, was evaluated in two large French and European studies and data on PK are now available. Results in VWD type 3 show no major differences in VWF:RCo and VWF:Ag for the concentrates that did or did not contain FVIII:C. As expected, the only difference was an approximate 6-hour delay in FVIII:C increase with the concentrate devoid of FVIII:C; therefore, administration of exogenous FVIII:C is recommended in type 3 VWD cases of acute life-threatening bleeding episodes or emergency surgeries. Clinical efficacy results of the French and European studies have been recently reported.

More recently, another VWF concentrate containing FVIII (Wilate) has been tested in PK and efficacy prospective studies. Data derived from PK and clinical studies have contributed to more appropriate use of VWF/FVIII concentrates. The specific activity of concentrates is important to derive the degree of VWF/FVIII product purity, whereas VWF:RCo/Ag and VWF:RCo/FVIII ratios can be considered markers of VWF/FVIII protein activity. The accumulation of FVIII:C that is exogenously infused together with that endogenously synthesized and stabilized by the infused VWF may cause very high FVIII levels when multiple infusions are given to cover major surgery. There is some concern that sustained high FVIII levels may increase risk of postoperative deep vein thrombosis (DVT); however, DVT is a rare event that has been reported only in VWD patients receiving repeated

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VWF/FVIII concentrate infusions to maintain clinical hemostasis after surgery. Therefore, when using repeated injections of VWF/FVIII concentrates for recurrent bleeding episodes and especially after major surgery, we suggest daily monitoring of FVIII:C levels and adjusting the VWF/FVIII concentrate dose to keep the patient's FVIII:C levels between 50 and 150 U/dL. The minimal VWF:RCo levels to maintain sufficient hemostasis in VWD have not yet been determined in prospective studies; however, preliminary retrospective data from a large cohort of well-characterized Italian VWD patients suggest that VWF:RCo levels over 30 U/dL are associated with a low incidence of spontaneous mucosal bleedings.

Finally, a preclinical trial in animals of recombinant VWF has been completed, and a phase I study is scheduled to begin soon. In my experience, patients have noticed that the treatment options for hemophilia A and VWD are not equivalent, so there is interest in the development of recombinant VWF for the treatment of VWD.

H&O Could you discuss bleeding prophylaxis in patients with VWD?

ABF Hemophilia patients, particularly pediatric patients, because of recurrent hematomas and epistaxis have been exposed to long-term primary prophylaxis for many years. Patients with VWD also may face long-term prophylaxis for the same reason. Dr. Erik Berntorp and colleagues investigated the use of Humate-P in children with severe VWD characterized by very low levels of FVIII. The patients who received the agent once or twice a week did not experience hematomas or epistaxis. In Italy, there is an ongoing prospective trial using Alphanate or Fanhdi in patients with severe gastrointestinal bleeding, hema-

triosis, or epistaxis, and patients are selected according to the frequency of recurrence of bleeding events. The trial is comparing prophylaxis to on-demand treatment. A similar prospective trial has been organized in many countries by the VWD International Prophylaxis study using Humate-P.

Suggested Readings

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