Treatment of Acquired von Willebrand Syndrome in Patients With Monoclonal Gammopathy of Uncertain Significance: Comparison of Three Different Therapeutic Approaches

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Patients with monoclonal gammopathies of uncertain significance (MGUS) may develop an acquired bleeding disorder similar to congenital von Willebrand disease, called acquired von Willebrand syndrome (AvWS). In these patients, measures to improve hemostasis are required to prevent or treat bleeding episodes. We diagnosed 10 patients with MGUS and AvWS: 8 had IgGκ (3) or λ (5) MGUS and 2 IgM-κ MGUS. Three therapeutic approaches were compared in them: (1) desmopressin (DDAVP), (2) factor VIII/von Willebrand factor (FVIII/vWF) concentrate, and (3) high-dose (1 g/kg/d for 2 days) intravenous Ig (IVIg). In patients with IgG-MGUS, DDAVP and FVIII/vWF concentrate increased factor VIII and von Willebrand factor in plasma, but only transiently. IVIg determined a more sustained improvement of the laboratory abnormalities and prevented bleeding during surgery (short-term therapy). In addition to the standard 2-day infusion protocol, a long-term IVIg therapy was performed in 2 patients with IgG-MGUS: repeated (every 21 days) single infusions of IVIg did improve laboratory abnormalities and stopped chronic gastrointestinal bleeding. On the other hand, IVIg failed to correct laboratories abnormalities in patients with IgM-MGUS. These comparative data obtained in a relative large and homogeneous group of patients with AvWS and MGUS confirm that DDAVP and FVIII/vWF concentrates improve the bleeding time (BT) and FVIII/vWF measurements only transiently, whereas IVIg provides a sustained treatment of AvWS associated with IgG-MGUS, but not with IgM-MGUS.

ACQUIRED von Willebrand syndrome (AvWS) is a rare bleeding disease similar to the congenital disease in terms of laboratory findings, being characterized by a prolonged bleeding time (BT) and low plasma levels of factor VIII-von Willebrand factor (FVIII/vWF).[1,2] About 100 cases of AvWS have been reported since the original description of a case in a patient with systemic lupus erythematosus.[3] Cases appear to be mainly associated with lympho-myeloproliferative disorders, immunologic diseases, and cancer.[1,2] About one third of the reported cases are associated with a monoclonal gammopathy of uncertain significance (MGUS).[3] The mechanisms of the vWF deficiency in AvWS are variable.[4] vWF is normally synthesized but is removed at an accelerated rate from plasma through four possible mechanisms[5]: (1) specific autoantibodies, (2) nonspecific antibodies that form circulating immune complexes and favor vWF clearance by Fc-bearing cells, (3) absorption onto malignant cell clones, and (4) increased proteolytic degradation.

In the absence of a consistent pathogenetic mechanism, treatment of the syndrome has usually been empirical. Aims of treatment are (1) removal of the underlying disorder, (2) control of the bleeding episodes, and (3) prevention of bleeding during surgery. In several disorders associated with AvWS, surgery, chemotherapy, radiotherapy, or immunosuppressive drugs can sometimes remove or control the underlying disease, with resolution of the bleeding diathesis and normalization of the laboratory abnormalities.[1,6] When the condition underlying AvWS cannot be removed or treated, such as MGUS, at least three approaches have been attempted to stop bleeding episodes and/or to prevent bleeding during surgery. Desmopressin (DDAVP) and/or plasma-derived FVIII/vWF concentrates have been effective in some cases,[7] but not in others.[5] High-dose intravenous Ig (IVIg) have been shown to be efficacious in several cases.[8-13] However, detailed studies comparing the effects of DDAVP and FVIII/vWF concentrates with those of IVIg are not available. Therefore, we organized a therapeutic trial in a relatively large and homogeneous group of patients with AvWS associated with MGUS, all treated on different occasions with DDAVP, an FVIII/VWF concentrate, or IVIg.

MATERIALS AND METHODS

Selection of the Patients

Between 1990 and 1996, 10 patients were referred to the Hemophilia and Thrombosis Center of Milano (Milan, Italy) or the Department of Hematology of Vicenza (Vicenza, Italy) for the onset of bleeding symptoms. During the same time period, 560 new patients with MGUS were diagnosed at both centers. MGUS was diagnosed after the onset of bleeding symptoms in all 10 patients. Patients' personal and family bleeding histories were negative. The main clinical and laboratory parameters are summarized in Table 1. All patients had mild or moderately severe bleeding symptoms, except patients no. 3 and 5, who had repeated episodes of gastrointestinal bleeding that required hospitalization and blood transfusions. Serum immunoelectrophoresis showed monoclonal components characterized as IgG or IgM, κ or λ. Levels of IgA, IgG, and IgM Igs were normal. Bence-Jones protein was undetectable. No evidence of excessive plasma cell infiltration was obtained at bone marrow examination. Other hematological measurements were normal. The serum levels of the monoclonal components remained stable over 72 months of follow-up, with no specific treatment.

Blood Sampling

Venous blood for hemostasis tests was drawn in 0.125 mmol/L citrate. For vWF multimeric analysis, blood was drawn into an anticoagulant and proteinase inhibitor mixture to final concentrations of

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Table 1. Main Clinical and Laboratory Parameters in Patients With MGUS and AvWS

Patient No.	Age*/ Sex	MGUS Type	Acquired Bleeding Symptoms
1	43/F	IgGλ	Menorrhagia
2	28/F	IgGκ	Hemoperitoneum for corpus luteum hemorrhage
3	57/F	IgGλ	Spontaneous and posttraumatic hematomas, epistaxis, menorrhagia, melena
4	36/F	IgGκ	Menorrhagia
5	66/M	IgGλ	Melena
6	72/M	IgGλ	Epistaxis
7	56/M	IgGκ	Epistaxis, bleeding after dental extraction
8	78/M	IgGλ	Epistaxis, posttraumatic hematoma
9	43/F	IgMκ	Gum bleeding
10	54/M	IgMκ	Epistaxis, gum bleeding

*Age in years at the presentation of bleeding.

0.125 mmol/L citrate, 5 mmol/L EDTA, 6 mmol/L ethylmaleimide, and 500 U aprotinin. Blood samples were centrifuged at 3,000*g* for 20 minutes to obtain platelet-poor plasma. For multimeric analysis, plasma was transferred to another tube and centrifuged at 40,000*g* for 20 minutes to remove residual platelets. All plasma were frozen in ethanol-dry ice and stored at −70°C until tested.

Criteria for von Willebrand Disease (vWD) Diagnosis and Characterization

The BT was measured by the Simplate II device (General Diagnostics, Morris Plane, NJ). vWF antigen (vWF:Ag) was measured by enzyme-linked immunosorbent assay (ELISA) and ristocetin cofactor activity (vWF:RCo) was measured by aggregometry of formalin-fixed platelets.[14] The vWF propeptide, known also as vWF antigen II, was measured by ELISA, using two monoclonal antibodies kindly provided by Dr C. de Romeuf (Laboratoire de Recherche sur l'Hemostase, Lille, France).[15] Platelet vWF was measured after platelet separation on Ficoll-Hypaque gradients and lysis with Triton X-100.[16] After centrifugation at 3,500*g* at 4°C for 10 minutes, supernatants were frozen at −80°C for vWF:Ag and vWF:RCo assays. Multimeric analysis was performed on low-resolution agarose gels.[17] All FVIII/vWF measurements were expressed in international units (IU), with reference to a plasma pool standardized against the International Reference Preparation for FVIII/vWF-related activities.

Anti-Factor VIII/vWF Inhibitor Characterization

The IgG fraction of the patients and normal controls were purified by affinity chromatography on Sepharose-Protein A (Pharmacia, Uppsala, Sweden).

Mixing studies. Normal plasma was mixed 1:1 vol/vol with patient plasma and incubated for 2 hours at 37°C. Samples were then centrifuged at 2,500*g* for 15 minutes and FVIII/vWF was measured in supernatants.

vWF-binding antibody assay. The assay was performed in IgG-MGUS cases according to Fricke et al.[18] In brief, serially diluted IgG purified from patient and normal plasma was bound to protein A and incubated with a constant amount of normal plasma. Residual FVIII/vWF activities were then measured on the supernatant of adsorbed plasma.

Inhibition of vWF binding to collagen. Binding of normal plasma vWF to collagen in the presence of normal or patient purified IgG was studied using an ELISA, as previously reported.[19]

Study Design

An open, crossover trial was performed between March 1995 and April 1997 at the two Hemophilia Centers of Milano and Vicenza. All patients received on different occasions three types of treatments: DDAVP (Emosint; Sclavo, Siena, Italy), an FVIII/vWF concentrate of intermediate purity (Haemate-P; Centeon, Marburg, Germany), or high-dose IVIg (Sandoglobulin [Novartis, Basilea, Switzerland] or Ig-Vena [Sclavo, Siena, Italy]). DDAVP and the FVIII/vWF concentrate were administered to all patients as test infusions with a wash-out time of at least 15 days, whereas IVIg was administered after we observed the unsatisfactory effect of these treatments to prevent or treat bleeding episodes. All subjects gave informed consent, and all of the experiments were performed in accordance with the Declaration of Helsinki.

Therapeutic Trials

DDAVP infusion. DDAVP was infused IV at a dose of 0.3 µg/kg, with blood samples and BT obtained before and 0.5, 1, 2, and 4 hours after the infusion of the drug.

FVIII/vWF concentrate infusion. Of the concentrate evaluated, 40 U/kg was infused, with blood samples and BT obtained before and 0.5, 1, 2, and 4 hours after infusion.

IVIg. A daily dose of 1 g/kg was infused for 2 days (Sandoglobulin [Novartis] or Ig-Vena [Sclavo]) before surgery, ie, multiple dental extractions (8 cases), parotid adenectomy (1 case), and abdominal surgery for hemoperitoneum (1 case). Blood samples and BT were obtained before and 1, 2, 4, 6, and 8 days from the beginning of the infusion (short-term therapy). In 2 patients (no. 3 and 5) with IgG-MGUS, single infusions of IVIg (1 g/kg) were repeated every 21 days, with blood samples obtained before and after each infusion for about 6 months (long-term therapy). Such repeated infusions were administered because, in these patients, recurrent gastrointestinal bleeding had led to severe anemia and frequent blood transfusion (>100 U of packed red blood cells within 1 year). In 1 case, the dosage of IVIg was tapered to 0.75 to 0.5 g/kg after several infusions, but the dosage was increased again to 1 g/kg when it became evident that this dosage was less effective.

RESULTS

Diagnosis of AvWS and Characterization of Anti-FVIII/vWF Inhibitors

Table 2 shows baseline values in patients with IgG-MGUS (8 cases) and IgM-MGUS (2 cases). The BT were prolonged, with values ranging from 10 to 23 minutes. FVIII:C levels were low but measurable (range, 9 to 36 U/dL). vWF:Ag levels were low in most patients (range, 3 to 37 U/dL). vWF:RCo was below the lower limit of detection of the method (6 U/dL) in all patients.

Table 2. Main Laboratory Measurements (Range) in Patients With MGUS and AvWS

Laboratory Measurements	IgG-MGUS (n = 8)	IgM-MGUS (n = 2)	Normal Controls (n = 20)
BT (min)	10-21	18-23	3-7
Factor VIII:C (U/dL)	9-36	20-36	62-156
vWF:Ag (U/dL)	3-16	26-37	52-148
vWF:RCo (U/dL)	<6	<6	49-151
vWF:propeptide (U/dL)	54-216	49-53	49-158
vWF (propeptide/Ag) ratio	7-51	1.3-2	0.7-1.9
High molecular weight multimers			
in plasma	Present	Absent	Present
in platelets	Present	Present	Present

There was some relationship between factor VIII/vWF measurements and the bleeding tendency, in that the 2 patients with recurrent melena had the lowest values of factor VIII:C and the longest BT. Despite low vWF levels, the vWF propeptide ranged from low borderline values to higher than normal values (range, 49 to 216 U/dL) in all 10 cases: propeptide levels were higher in IgG-MGUS (range, 54 to 216 U/dL) than in IgM-MGUS (range, 49 to 53 U/dL), with a high vWF propeptide/Ag ratio. The multimeric pattern of plasma vWF was normal in all the 8 cases with IgG-MGUS, whereas high molecular weight forms were lacking in IgM-MGUS (Table 2).

Platelet vWF

Platelet vWF:Ag and vWF:RCo were normal in all cases, with mean values of vWF:Ag of 38 IU/10^9 platelets and vWF:RCo values of 30 IU/10^9 platelets. The platelet multimeric pattern was similar to that obtained in platelets from normal individuals (not shown).

Inhibitors of FVIII/vWF

No evidence of inhibitors against any of the FVIII/vWF measurements was found in the majority of the patients, by mixing studies, vWF-binding antibody assay, and inhibition of vWF binding to collagen. A mild anti-FVIII activity (0.5 BU) was found in 1 case of IgM-MGUS and a mild anti-vWF:RCo was found in 1 case of IgG-MGUS λ (2 anti-vWF:RCo units).

Therapeutic Trials

Effects of DDAVP. The effects of *DDAVP* on the BT and FVIII/vWF measurements, summarized as mean values, are shown in Fig 1A for IgG-MGUS and Fig 1B for IgM-MGUS. In IgG-MGUS and in IgM-MGUS, all the FVIII/vWF measurements increased after DDAVP but rapidly decreased to return close to baseline values by 4 hours; the mean BT was shortened for 1 hour but then returned to abnormal values.

Effects of FVIII/vWF concentrate. The effects of FVIII/vWF concentrate infusions, summarized as mean values, are shown in Fig 2A for IgG-MGUS and Fig 2B for IgM-MGUS. In IgG-MGUS and IgM-MGUS, the BT shortened without normalizing immediately after concentrate administration but returned to baseline at 4 hours. All the FVIII/vWF measurements were transiently corrected for 1 hour to return close to baseline values by 4 hours. In the patient with mild anti-FVIII inhibitory activity, the postconcentrate FVIII:C response was lower than the vWF:RCo response (not shown).

Effects of IVIg, short-term therapy. The effects of high-dose (1 g/kg/d for 2 days) IVIg, summarized as mean values, are shown in Fig 3A for IgG-MGUS and Fig 3B for IgM-MGUS. In IgG-MGUS, 1 day after the second infusion, the BT and FVIII/vWF measurements progressively normalized reaching the maximal effect on day 4. The BT then remained close to normal values and FVIII/vWF measurements ranged between 35 and 55 U/dL until day 18, to return to preinfusion values after 21 days (see later Fig 4). In IgM-MGUS, the infusion of the same dose of IVIg was accompanied by a modest shortening of the BT and a poor increase of FVIII/vWF levels within the first week of therapy (Fig 3B), with a return of BT and plasma FVIII/vWF activities to abnormal baseline values after 15 days (not shown).

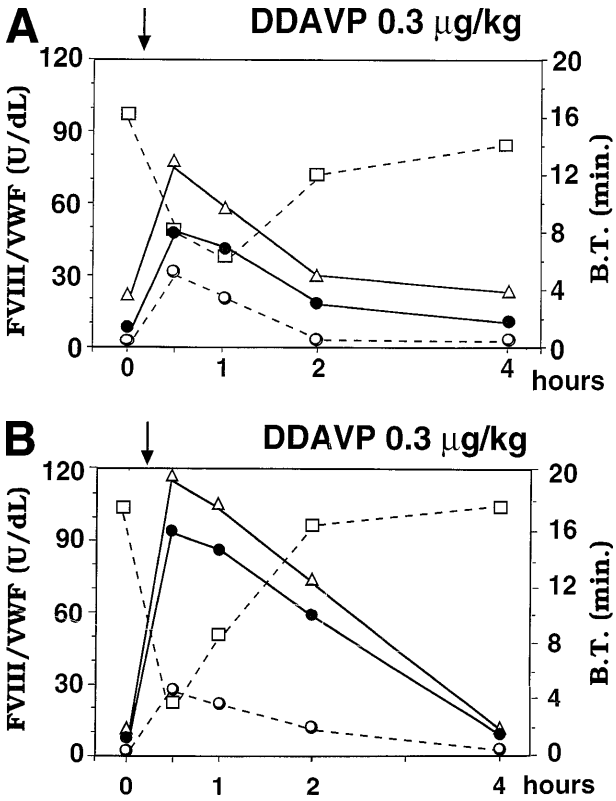

Fig 1. Effect of DDAVP (0.3 μg/kg) IV infusion to 8 patients with IgG-MGUS (A) and 2 patients with IgM-MGUS (B). Mean values of bleeding time (BT) and FVIII/vWF measurements ([□] BT; [△] FVIII; [●] vWF:Ag; [○] vWF:RCo) before (0) and at various times after the infusion of DDAVP.

Effects of IVIg, long-term therapy. In patients no. 3 and 5 with IgG-MGUS and severe recurrent gastrointestinal bleeding, after the loading dose of 1 g/kg for 2 days, repeated single infusions (1 g/kg) of IVIg were effective in improving the BT and FVIII/vWF levels, with return to baseline levels in about 3 weeks. In both patients, gastrointestinal bleeding stopped and blood transfusions were no longer required during the following 24 months. In patient no. 3 (Fig 4), lower dosages (0.5 g/kg) were attempted but did not achieve the same effects on laboratory measurements. Transient improvement of these measurements was achieved again when a dosage of 1 g/kg was administered (Fig 4).

DISCUSSION

MGUS is a relatively frequent cause of AvWS (approximately one third of all the cases), so that it is appropriate to search for vWF abnormalities in patients presenting with acquired bleeding symptoms. On the other hand, in our two centers, only 10 of 560 cases with MGUS seen over 7 years developed AvWS accompanied by significant bleeding symptoms, so that it is probably not appropriate to screen MGUS patients for AvWS in the absence of bleeding symptoms. This is the first study that compares the laboratory response to three different therapeutic approaches in a relatively large number of patients with AvWS associated with IgG-MGUS or IgM-MGUS.

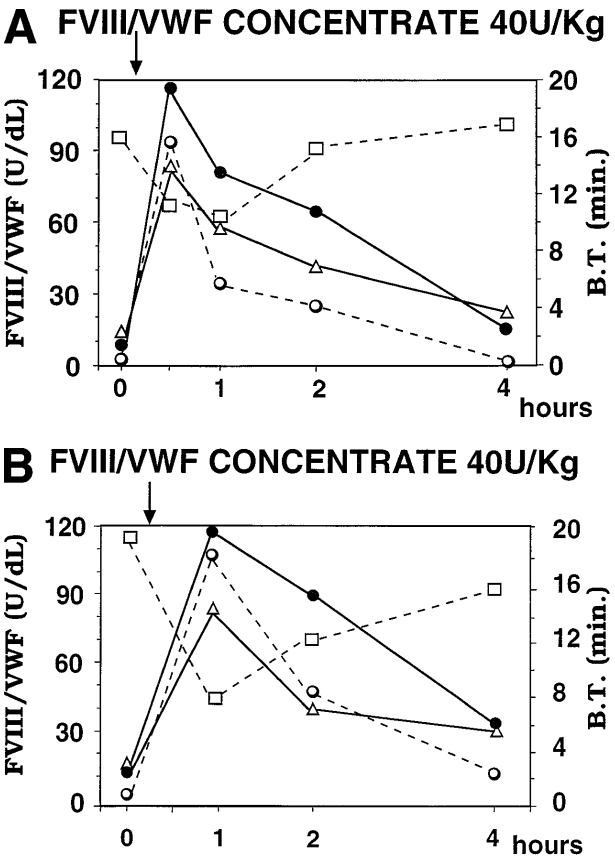

Fig 2. Effect of an FVIII/vWF concentrate (Haemate-P; 40 U/kg) IV infusion to 8 patients with IgG-MGUS (A) and 2 patients with IgM-MGUS (B). Mean values of BT and FVIII/vWF measurements ([□] BT; [△] FVIII; [●] vWF:Ag; [○] vWF:RCo) before (0) and at various times after concentrate infusion.

In agreement with a diagnosis of AvWS, vWF and FVIII plasma levels were very low. Platelet vWF concentrations and structure were normal.[5] The only clear laboratory differences between IgG-MGUS and IgM-MGUS were the multimeric structure of plasma vWF and the levels of the vWF propeptide. Whereas baseline levels of plasma vWF propeptide were normal or higher than normal in all patients, the vWF: propeptide/Ag ratio was higher than normal in IgG-MGUS but normal in IgM-MGUS. A high vWF:propeptide/Ag ratio has been proposed by Scott et al[20] as a simple method to distinguish AvWS due to decreased vWF synthesis from that due to increased clearance. There was a normal multimeric pattern in IgG-MGUS cases, as reported previously,[5] but a selective loss of large and intermediate multimers in the 2 IgM-MGUS cases, as reported in other clinical conditions associated with AvWS.[1,2] The observed differences in multimeric pattern and vWF: propeptide/Ag ratios suggest that different pathogenetic mechanisms underlie the AvWS associated with IgM-MGUS and IgG-MGUS, even though we failed to identify such mechanisms. In the majority of patients no inhibitory activity of the monoclonal protein of these patients could be demonstrated in vitro: mild anti-FVIII activity was present only in 1 case with IgM-MGUS and anti-vWF:RCo in 1 case with IgG-MGUS. There was no inhibitory activity of vWF to collagen, previously described in a patient with AvWS.[21]

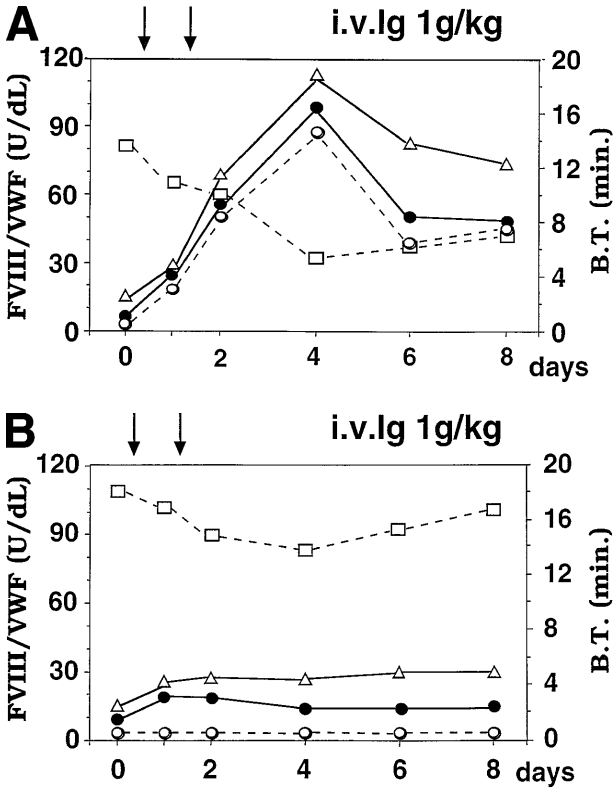

Fig 3. Effect of high-dose Ig therapy in 8 patients with IgG-MGUS (A) and 2 patients with IgM-MGUS (B). BT and FVIII/vWF measurements ([□] BT; [△] FVIII; [●] vWF:Ag; [○] vWF:RCo) before and at various times after Ig infusion. Mean values of the patients are indicated.

However, even though no inhibiting activity was demonstrated in most of our MGUS cases, the rapid clearance of endogenous vWF after DDAVP and of exogenous vWF after FVIII/vWF concentrate (without the sustained increase of FVIII

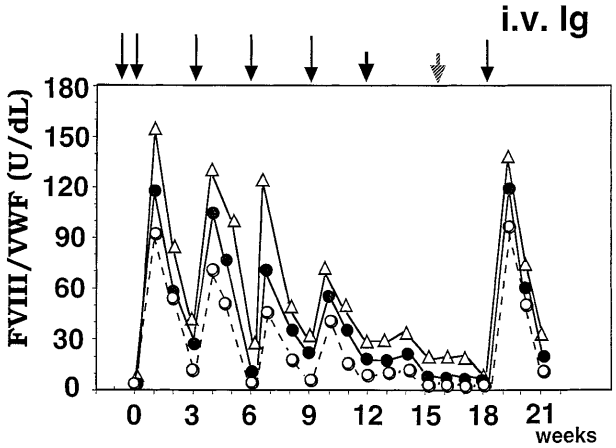

Fig 4. Representative example of long-term Ig therapy in a patient with IgG-MGUS FVIII/vWF measurements ([△] FVIII; [●] vWF:Ag; [○] vWF:RCo) before and at various times after repeated infusion of high-dose Ig. Arrows at the top indicate the infusion of different concentrations of Ig: 1 g/kg (solid, long arrow), 0.75 g/kg (solid, short arrow), and 0.5 g/kg (hatched, short arrow). Note that the response of FVIII/vWF measurements is consistent when 1 g/kg Ig is used but is lower when the dosage is tapered.

usually seen in patients with congenital vWD) supports the hypothesis that the monoclonal protein binds vWF in vivo.

All of the patients enrolled in this study received sequentially DDAVP, a FVIII/vWF concentrate, and IVIg. After DDAVP and the FVIII/vWF concentrate, the BT and FVIII/vWF measurements did improve but only transiently. In most of the cases, BT and factor VIII/vWF measurements returned to baseline levels within 2 hours (Figs 1 and 2A and B). In agreement with previous reports,[8-13] two single daily IVIg infusions (short-term therapy) induced a prompt and sustained normalization of FVIII/vWF activities and of the BT for at least 15 days in all IgG-MGUS (Fig 3A). However, in IgM-MGUS, the same treatment did not improve substantially the laboratory measurements.

The mechanisms of therapeutic action of IVIg have not been completely elucidated.[22] Some indicate a role for the anti-idiotype antibodies contained in the Ig preparation.[23] This hypothesis is tenable for acquired FVIII inhibitors but not for AvWS associated with MGUS, because no autoantibodies could be demonstrated in our patients before treatment. Two alternative hypotheses, ie, blockade of Fc-receptors on the reticulo-endothelial system or elimination of circulating immune complexes by monomeric Ig, might be more suitable to explain the efficacy of IVIg in IgG-MGUS.

In patients with IgG-MGUS, the high-dose IVIg regimen was effective not only as a single infusion to prepare patients for surgery, but also as long-term therapy to stop chronic gastrointestinal bleeding or prevent bleeding recurrency. Repeated doses of IVIg administered every 21 days produced consistent responses on FVIII/vWF measurements and clinical remission of the bleeding diathesis. To our knowledge, few cases of prolonged IVIg treatments have been reported.[9,10] One of these patients became refractory after the successful increase of vWF:RCo obtained with the first course of IVIg.[9]

The dosage of 1 g/kg seems to be critical, because smaller or no responses were elicited in 1 patient when the dosage was tapered to 0.75 and 0.5 g/kg. The good response obtained again when the dosage of 1 g/kg was administered excludes resistance to immunoglobulins. One obstacle for the prolonged therapy with IVIg is the high cost of treatment. In our series, long-term therapy was limited only to patients who were chronically bleeding and required a high rate of blood transfusion (>100 U of packed red blood cells in 1 year), with high costs due to hospitalization and high risks of blood-borne infections.

In conclusion, we have demonstrated that in the AvWS associated with MGUS the response to treatments such as DDAVP and plasma FVIII/vWF concentrate is poor in cases of IgG-MGUS and only transient in cases of IgM-MGUS. The infusion of high-dose IVIg, although expensive, induces transient (short-term therapy) and prolonged (long-term therapy) clinical and laboratory remission in IgG-MGUS but not in IgM-MGUS. Therefore, IVIg therapy cannot be used in all cases of AvWS but must be recommended in selected cases with AvWS associated with IgG-MGUS.

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