Are intravenous immunoglobulins really inappropriate in acquired von Willebrand syndrome?

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Dear Sir,

We read with great interest the "Recommendations for the use of albumin and immunoglobulins" by Liumbruno and colleagues on behalf of the Italian Society of Transfusion Medicine and Immunohematology (SIMTI), recently published in Blood Transfusion[1]. We noted that acquired von Willebrand syndrome (AVWS) is listed in Table III among the inappropriate indications for the use of intravenous immunoglobulins (IVIG). Although the reported level of evidence is particularly low (2C), we do not agree with such a strong statement. In fact, according to our direct experience with AVWS patients for the last 20 years, we believe that IVIG should actually be considered at least as an useful additional therapeutic approach for the management of bleeding of these patients[2-5].

AVWS is a rare bleeding disorder similar to inherited von Willebrand's disease in terms of laboratory findings and clinical severity. It is characterised by a prolonged bleeding time and variably low plasma levels of von Willebrand factor (VWF) and factor VIII (FVIII). The syndrome usually occurs in individuals with no personal or family history of bleeding**.** Since the original description of AVWS in 1968, in a patient with systemic lupus erythematosus[3,5], more than 300 cases of AVWS have been reported. Several review articles have been published**,** and data from an International Registry on AVWS are also available[3]. Six categories of underlying disorders have been reported to occur frequently in patients with AVWS: lymphoproliferative and myeloproliferative disorders; solid tumours; immunological and cardiovascular disorders; and miscellaneous conditions. Taken together, lymphoproliferative and myeloproliferative disorders appear to be most frequently associated with AVWS in both the literature and the registry, accounting for 48-63% of cases[3]. However, in a retrospective study Thiede *et al.* found a relatively high association with cardiovascular disorders (46%) in comparison to monoclonal gammopathy (31%), which is usually reported as the most frequent underlying disorder[5].

Data from large prospective studies are not available and the actual prevalence of AVWS in the general population is, therefore, unknown. In the only prospective study available, the prevalence was approximately 10% in 260 patients with haematological disorders enrolled by a single institution[5]. According to these observations, the number of patients with AVWS is certainly underestimated, because most AVWS patients do not bleed until they are exposed to major trauma or major invasive procedures and surgery[5]. Compared with acquired haemophilia A, which is always due to auto-antibodies against FVIII, a variety of pathogenic mechanisms have been proposed to cause structural or functional disturbances of VWF[3,5]. These include autoantibodies, either interfering with platelets or collagen binding or increasing VWF clearance from the plasma[5]. Sequestration of high-molecular weight multimers was demonstrated in patients with haematological disorders due to adsorption to myeloma cells or platelets, but also in reactive thrombocytosis. Proteolytic cleavage of VWF can occur after shear stress-induced unfolding, and AVWS due to this mechanism was described in disorders with increased shear stress, in particular aortic valve stenosis and left ventricular assist devices. Proteolytic cleavage has also been described in patients with pancreatitis, liver cirrhosis and leukaemia and in those taking certain medications. In hypothyroidism, AVWS seems to result from decreased synthesis of otherwise normal VWF[5].

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The management of AVWS is targeted in two main directions: treatment of the underlying medical condition (with surgery, chemotherapy, radiotherapy and/or immunosuppressants), which can result in remission of AVWS, and correction of the acute bleeding episode[3,5]. The treatment options for this latter purpose include desmopressin, VWF-containing concentrates, plasmapheresis, recombinant factor VIIa and IVIG[3,5]. In particular, the clinical use of IVIG in AVWS has been described by several authors[2,5], and the results from the International Registry reported an overall success rate of 33% (21 of 63 cases) for this treatment, which was more effective in lymphoproliferative disorders (18 [37%] of 48), solid tumours (2 [100%] of 2) and immunological diseases (1 [50%] of 2)[3]. IVIG seem to be especially useful in AVWS cases associated with monoclonal gammopathy of undetermined significance (MGUS)[2,5]. In the prospective trial, which enrolled 10 patients with AVWS and MGUS, IVIG were more effective than desmopressin or VWF/FVIII concentrates because they induced a prompt and sustained increase of FVIII/VWF activities and shortened the bleeding time for at least 15 to 20 days in all IgG-MGUS cases. By contrast, no response was observed in AVWS patients with MGUS of the IgM class (IgM-MGUS) [2]. The mechanism of action of IVIG in this setting is unclear but could involve an anti-idiotype effect, blockage of reticulo-endothelial Fc-receptors or elimination of circulating immune complexes by circulating immunoglobulin[2,4].

In conclusion, the published literature document that IVIG are an important therapeutic option for the management of AVWS cases, especially those associated with IgG-type monoclonal gammopathies. As a consequence, we suggest that the next revision of the recommendations will take in account our comments and that AVWS will be included in the list of non-recognised conditions in which IVIG have been used with some benefit.

The Authors declare no conflicts of interest.

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