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**A ROLE FOR INTRAVENOUS IMMUNOGLOBULIN IN THE TREATMENT OF ACQUIRED VON WILLEBRAND SYNDROME ASSOCIATED WITH IGM GAMMOPATHY.**

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**LETTER TO THE EDITOR:**

Acquired Von Willebrand Syndrome (AVWS) is a rare bleeding disorder resulting from reduction in plasma von Willebrand Factor (VWF) in patients with no previous personal or family history of Von Willebrand Disease (VWD). AVWS may present with significant bleeding, complicated by short-lived responses to DDAVP or VWF-containing concentrate. AVWS is commonly associated with cardiovascular and lymphoproliferative disorders (LPDs) [1]. Amongst the LPDs, monoclonal gammopathy of undetermined significance (MGUS) is the most frequent association. Haemorrhage in MGUS-AVWS may be both spontaneous and severe. Treatment options include DDAVP, tranexamic acid and VWF-containing concentrates however patient co-morbidities, age or poor clinical and laboratory responses often restrict use [2]. Furthermore, individual responses following DDAVP and VWF-containing concentrates are highly variable and response duration may be short [1]. Consequently, the management of bleeding in patients with MGUS-AVWS presents a significant clinical challenge. Multiple second-line therapeutic approaches have been explored including intravenous immunoglobulin (IVIg) [3], plasmapheresis [4] and immunomodulatory drugs such as lenalidomide [5]. While definitive treatment of the underlying LPD may induce AVWS remission, treatment for MGUS is not usually warranted.

A single trial has evaluated responses to IVIg in MGUS-AVWS patients (8 IgG MGUS, 2 IgM MGUS) [6]. Administration of IVIg (1g/kg for two days) induced a sustained increase in plasma VWF levels for patients with IgG MGUS-AVWS.

Plasma VWF responses peaked at day 4 post IVIg treatment, returned to baseline by 21 days and regular fortnightly infusions maintained plasma VWF levels. In contrast however, no significant responses to IVIg were observed in the two patients with IgM MGUS [6]. Use of IVIg has been reported in only two other patients with IgM MGUS-AVWS, with a similar lack of efficacy seen [7]. On the basis of these findings, IVIg has been widely reported to be ineffective in patients with IgM MGUS-AVWS [3,6,7].

Given the heterogeneous pathogenic mechanisms involved in MGUS-AVWS, we hypothesised that IVIg may be useful in some patients with IgM MGUS-AVWS. Herein, we report both beneficial clinical effects and sustained correction of plasma VWF levels following IVIg in two patients with IgM MGUS-AVWS. Interestingly, IVIg appeared to reverse different pathological mechanisms in the two cases. In P01, IVIg therapy corrected a previously markedly elevated VWF:pp/VWF:Ag ratio, consistent with an IgM-mediated enhanced VWF clearance phenotype. In contrast, in P02 there was no evidence of enhanced VWF clearance. Collectively these results are of direct clinical importance, highlighting that IVIg may be of clinical utility in the management of bleeding complications in some patients with IgM MGUS-AVWS.

All VWF, Factor VIII (FVIII:C) and mixing assays were performed on platelet poor plasma collected in sodium citrate (3.2%) (0.106M) and compared to established laboratory reference intervals. VWF:RCo-based mixing studies in both patients did not demonstrate the presence of an inhibitor. VWF:Ag levels were measured using a latex particle enhanced immunoturbidimetric assay (HemosIL<sup>®</sup> assay, Instrumentation Laboratories, IL, Italy) on an automated coagulometer (ACLTop700, IL, Italy). VWF:RCo levels were determined by standard platelet agglutination

(Sysmex CS2100i Analyser, Siemens Healthcare, Germany); Factor VIII (FVIII:C) levels measured using one-stage clotting assay (ACLTop700, IL, Italy) and monoclonal bands using serum protein electrophoresis. Plasma VWF propeptide (VWF:pp) levels were determined as previously described and the plasma VWF half-life was derived [8].

P01, a 60 year old male, underwent a sibling allogeneic bone marrow transplantation for Sezary syndrome. He subsequently developed a post-transplant lymphoproliferative disorder manifested by a small IgM paraprotein. Following removal of a central venous catheter, he developed persistent haemorrhage from the catheter-insertion site despite no preceding personal or family bleeding history. Laboratory workup identified markedly reduced plasma VWF parameters (VWF:Ag 20IU/dL, VWF:RCo <10IU/dL, FVIII:C 22IU/dL, Table 1). One hour post VWF concentrate (Wilate® 50IU/kg; Octapharma), plasma VWF:Ag and VWF:RCo levels were 153IU/dL and 64IU/dL respectively, and bleeding resolved. However, 4 hours post treatment, the plasma VWF:RCo level had fallen to only 18IU/dL (Figure 1A). The patient's clinical course was complicated by further bleeding, including a significant ankle haemarthrosis following a minimal episode of trauma. In an effort to provide a sustained increase in plasma VWF levels, IVIg therapy (1g/kg for 2 days) was administered. Interestingly, P01 had a significant and sustained VWF response following IVIg administration (Figure 1B). Peak plasma VWF levels were observed 48-72 hours after infusion, with a subsequent decline in VWF levels over the next 5-7 days. To define the biology underlying the efficacy of IVIg in this patient, plasma VWF propeptide (VWF:pp) levels were investigated. At steady state, plasma VWF:pp/VWF:Ag ratio was markedly elevated at 10.68, consistent with significantly

enhanced VWF clearance. However, following administration of IVIg, the plasma VWF:pp/VWF:Ag ratio fell to 1.62. Moreover, the VWF:pp/VWF:Ag ratio gradually increased the effect of IVIg started to wane (Figure 1C). Based on these findings, P01 was maintained on fortnightly IVIg therapy, resulting in sustained improvement in plasma VWF levels and resolution of all bleeding complications.

P02, a 65 year old male, presented with significant epistaxis and gastrointestinal bleeding necessitating multiple transfusions despite no previous personal or family history of bleeding. Laboratory workup demonstrated reduced plasma VWF activity (VWF:Ag 54IU/dL, VWF:RCo 29IU/dL, FVIII:C 56IU/dL, Table 1) and a small IgM monoclonal band (1.4g/L). Interestingly, the plasma VWF:pp/VWF:Ag ratio was not increased in P02 (1.49), suggesting that the reduction in his plasma VWF levels was not primarily attributable to enhanced clearance. Consistent with this hypothesis, P02 had a sustained response following treatment with VWF concentrate (plasma VWF:RCo 80IU/dL at 4 hours post 25 IU/kg Fandhi®, Grifols - Figure 1A; VWF:RCo 62IU/dL at 24 hours post). Furthermore, IVIg (1g/kg for 2 days) administration also resulted in a significant sustained increase in plasma VWF:Ag and VWF:RCo (Figure 1D). IVIg was subsequently administered for treatment of epistaxis and prior to dental extractions with an excellent, early laboratory and clinical response (peak VWF:RCo 85IU/dL, day 2).

AVWS often results in a significant bleeding phenotype, as evidenced in our two patients. Although DDAVP may improve plasma VWF levels, we do not commonly use DDAVP in patients >55 years in our centre. With VWF concentrate plasma VWF levels increased in both patients, however for P01 this was short lived. In contrast to

previous reports [6,7] totalling four patients with IgM MGUS-AVWS, our data clearly shows that IVIg may induce both a clinical and laboratory response in patients with IgM MGUS-AVWS. In these previous reports the individual paraprotein burden was not described. Of interest, in both our patients the absolute IgM paraprotein burden was low; this may contribute to the response seen.

The biological mechanisms resulting in AVWS are heterogeneous, even within patients with the same underlying cause. We observed the differing impact of the monoclonal protein in P01 and P02, with enhanced plasma VWF clearance evidenced in P01 (baseline VWF:pp/VWF:Ag ratio 10.68) but not P02 (VWF:pp/VWF:Ag ratio 1.49). Given the significant discrepancy between VWF:RCo and VWF:Ag, it seems likely that the IgM antibody in this patient is specifically interfering with the functional interaction between VWF and platelets. Nevertheless, our findings suggest IVIg may be considered as potential therapeutic option for at least some patients with IgM MGUS-AVWS. Due to the inter-individual variability in response, frequent monitoring of both plasma VWF:Ag and VWF:RCo levels is advised in all patients with AVWS undergoing treatment. Further studies are required to elucidate the biological mechanisms through which IVIg acts in IgM MGUS-AVWS.

**AUTHORSHIP:**

Contribution: M.L., M.B. and J. S. O'D. analyzed the data. All authors (M.L., B.W., K.R., M.B., N.M.O'C. and J. S. O'D.) were involved in writing and reviewing the paper

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The authors have no competing interests.

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