# Use of Vonicog Alpha and Acquired von Willebrand Syndrome, a New Approach: A Case Report

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## Abstract

Therapeutic management of acquired von Willebrand syndrome (AVWS) can be challenging, particularly in cases of AVWS associated with monoclonal IgM such as Waldenström macroglobulinemia (WM) where several therapeutic options may be ineffective. Here, we describe the case of an 88-year-old patient who developed AVWS during follow-up for WM. The presence of a severe bleeding symptomatology not controlled by several therapies (plasma-derived von Willebrand factor, plasmapheresis) led us to introduce a supplementation with recombinant von Willebrand factor, vonicog α (Veyvondi, Takeda, Japan), starting at a dose of 50 IU/kg/d. This supplementation allowed clinical (no further bleeding) and biological (hemoglobin level, von Willebrand factor parameters) improvements. Because of the persistence of bleeding risk factors, the treatment was maintained at a prophylactic dose (20 UI/kg three times a week), without recurrence of bleeding events for a period of 9 months.

**Keywords**
- von Willebrand disease
- Waldenström macroglobulinemia
- prophylaxis
- von Willebrand factor

## Introduction

Acquired von Willebrand syndrome (AVWS) is a rare but potentially serious bleeding condition that affects primary hemostasis. Clinically and biologically, it is similar to congenital von Willebrand disease (VWD) and it is characterized by loss of von Willebrand factor (VWF). AVWS can result from four pathogenic mechanisms: enhanced clearance (due to binding of autoantibodies), adsorption on malignant cells, increased proteolysis, or decreased synthesis.[1]

AWVS can be secondary to many underlying disorders among solid and hematological cancers, autoimmune or cardiovascular disorders.[1] However, it is mostly associated with lymphoproliferative diseases such as monoclonal gammapathy of undetermined significance or, less frequently, Waldenström macroglobulinemia (WM). WM is a B cell neoplasm resulting from the accumulation of clonal lymphoplasmacytic cells secreting a monoclonal immunoglobulin (Ig) M protein.

Treatment of AVWS is based on three points: treatment of the underlying pathology, bleeding control, and prevention of further bleedings.[2] For bleeding control, several strategies may be considered depending on the underlying disorders.[3] Use of desmopressin (DDAVP) or replacement therapies (plasma-derived VWF [pdVWF]/factor [F] VIII) have been tested with low or moderate efficacy because of enhanced

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clearance due to autoantibodies or proteolysis. In lymphoproliferative neoplasms, plasmapheresis or intravenous immunoglobulin (IVIg) aims at eliminating or inhibiting autoantibodies. Unfortunately, IVIg option has poor efficacy in case of IgM antibodies as in WM. A by-passant agent such as recombinant activated factor VII (rFVIIa) can be used in that latter case or when VWF is adsorbed on cells. As in congenital VWD, antifibrinolytics are very helpful in adjunction with previous therapies. However, sometimes these approaches may be insufficient, and development of new therapies is awaited. Here, we describe a case of AVWS associated with WM effectively managed by curative and prophylactic regimen with recent recombinant VWF (rVWF), vonicog α (Veyvondi, Takeda, Japan), in view of data in the literature showing the low effectiveness of other treatments for this type of AVWS.

## Case Report

An 88-year-old patient was admitted in April 2021 to the emergency room of our hospital.

He had been diagnosed 3 years earlier with WM in another hospital. The diagnosis was made because of an aregenerative normocytic anemia (hemoglobin: 105 g/L, MGV: 95 µm$^3$, reticulocytes: 41G/L). Serum protein electrophoresis showed a peak in the β-globulins estimated at 37.6 g/L. Immunofixation confirmed the presence of a monoclonal component IgM κ. Bone marrow was infiltrated by 55% of lymphocytes, often with lymphoplasmacytic differentiation. Immunophenotyping confirmed the diagnostic of WM (monotypic population CD5$^-$ CD10$^-$ CD23$^-$ fmc7$^-$ CD79B$^+$ CD22$^+$ CD43$^+$).

During his follow-up, he was referred to the hemostasis consultation because of recurrent hematomas. Blood tests revealed an isolated anemia (hemoglobin: 100 g/L, MGV: 95 fL) and isolated VWF defect: prothrombin time (PT): 77%, activated partial thromboplastin time (APTT) ratio: 1.35, fibrinogen: 2.7 g/L, FVIII: C 31 IU/dL, FIX: C 96 IU/dL, FXI: C 78 IU/dL, VWF antigen (VWF:Ag) 21 IU/dL, VWF activity (VWF:Act) 16 IU/dL. The biological results are summarized in ►Fig. 1. Anti-VWF antibodies detection was negative (ELISA). As the patient had no personal (albeit several surgical procedures without bleeding) or familial history of bleeding, he was diagnosed with AVWS.

Because of persistence of frequent skin bleedings, a treatment for WM was initiated. The patient received several lines of chemotherapy started in July 2020 (chloraminophene, rituximab-cyclophosphamide, bendamustine, bortezomib) without clinical efficacy: the IgM κ level went from 42.2 to 71.9 g/L in 9 months. During follow-up, one episode of epistaxis required treatment with pdVWF and tranexamic acid (1 g three times a day, no more information available on this episode and notably the effectiveness of the treatments).

Upon arrival at the emergency room of our hospital in April 2021, the patient presented bleeding from elbow and auricle wounds, and multiple hematomas. Moreover, he was

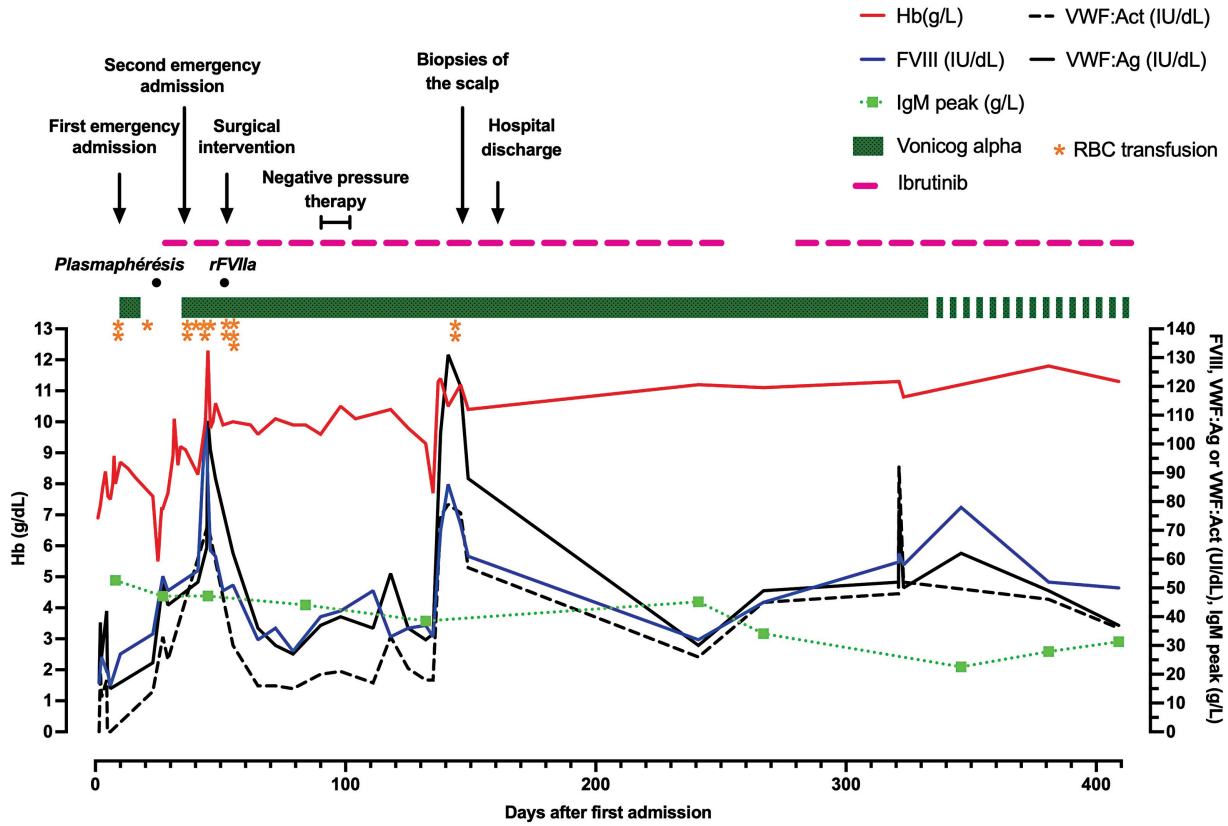


**Fig. 1** Evolution of biological results according to treatment and clinical events. Description of changes in biological parameters: hemoglobin (red line), FVIII (blue line), VWF:Ag (black line), VWF:Act (black dotted line), and monoclonal IgM (light green square and light green dotted line) as a function of clinical events (black arrows, black dots) and drug treatments: ibrutinib (pink dotted line) and vonicog α (green rectangles).

 

anemic (hemoglobin had fallen from 83 to 69 g/L in 6 days) and thrombopenic (platelets: 56 g/L). Clinically, the patient had arterial hypotension (BP: 90/51) without tachycardia (HR: 69 bpm). Hemostasis blood tests showed a severe deficit in VWF:Ag 17 IU/dL, VWF:Act <11 IU/dL, FVIII:C 17 IU/dL (no other complementary examination could be performed due to the small volume of plasma collected before treatment). He received a symptomatic treatment with red blood cell transfusion. We immediately initiated a replacement treatment with rVWF (vonicog α, 50 IU/kg/d for 3 days). As described in the literature, the half-life of pdVWF can be very short in acquired VWD.[3] We made the hypothesis that we would have a better recovery with vonicog α due to the presence of high-molecular-weight (HMW) multimers. A plasmapheresis was planned in addition but failed during the second attempt because of venous access issues. A week after admission, ibrutinib (Imbruvica, Janssen, Belgium) was introduced to treat WM. Hemostasis blood test results were as follows, respectively, 1 and 6 hours after the third rVWF injection: VWF:Ag 42 and 22 IU/dL, VWF:Act 18 and <11 IU/dL, FVIII:C 21 and 21 IU/dL. These results are compatible with an increased turnover of VWF. Bleeding eventually stopped despite a poor biological response and the patient was discharged from hospital.

The patient was readmitted 1 week later after a fall. He presented multiple head wounds, right arm hematoma, and active bleeding on the right hand. On admission, hemoglobin level was 76 g/L. A similar treatment was initiated with red blood cell transfusions and replacement therapy with vonicog α (50 IU/kg once a day for 21 days). Residual values after 6 days of treatment (i.e., 24 hours post-infusion) were as follows: VWF:Ag 44 IU/dL, VWF:Act 25 IU/dL, FVIII 49 IU/dL. The severe active bleeding of the right hand amended progressively and allowed the cessation of red blood cell transfusions. However, the hematoma of the right arm became a large dissecting hematoma that required surgical management. Injection of recombinant activated FVII (5 mg, 3 bolus) in addition to vonicog α was necessary to control surgery-induced bleeding. Because of the need for negative pressure therapy for healing which increased the risk of bleeding, treatment by vonicog α was increased (85 IU/kg/d) without recurrence of significant bleeding.

The patient then underwent biopsies of the scalp because of skin lesions that revealed a squamous cell carcinoma. The presence of these high-risk bleeding lesions together with the patient's risk of falls led the team to allow discharge on vonicog α prophylaxis (20 IU/kg/d) which was then reduced to 20 IU/kg three times a week after 6 months. Forty-eight hours after injection, residual hemostasis blood tests were as follows: VWF:Ag 50 IU/dL, VWF:Act 52 IU/dL, FVIII:C 58 IU/dL. Apart from two minor epistaxis which ceased under tranexamic acid, no other bleeding episode was noted.

To date, the patient is still under prophylaxis with vonicog α with a 9-month follow-up. Treatment with ibrutinib for WM is ongoing with low efficiency so far (IgM peak level remains around 20–30 g/L) and radiotherapy sessions are scheduled for squamous cell carcinoma.

## Discussion and Conclusion

We present here a case study of treatment of AVWS with recombinant VWF (vonicog α) which enabled the resolution of the severe hemorrhagic syndrome. The treatment was maintained as a prophylactic regimen. To our knowledge, it is the first report of prophylactic use of vonicog α in AVWS.

Previously three teams had reported the successful use of vonicog α in the management of surgery or bleeding in AWVS. Weyand et al reported the use of vonicog α in a child with AVWS associated with pulmonary valve stenosis who required cranioplasty following a skull fracture.[4] Höpting et al described the case of a patient with IgM-associated MGUS treated with recombinant factor Willebrand for acute bleeding episodes.[5] Recently, Heubner et al published the case of an adolescent undergoing ECMO in the context of COVID-19, who developed AVWS. Administration of vonicog α resulted in improvement of bleeding.[6]

Treatment of acquired VWD associated with WM remains challenging because of specific features of the disease. Use of polyclonal immunoglobulin has been shown ineffective in most IgM class monoclonal gammapathy, unless the IgM level was low.[1,7] Plasmapheresis has proven their effectiveness, but in the case reported here, it was not possible because of venous access limitation. Use of pdVWF is often limited in AVWS: because of accelerated clearance of VWF, pdVWF is expected to have a shortened half-life in AVWS. To overcome this problem, Dane et al described a successful continuous infusion of von Willebrand concentrate in three patients with IgG MGUS-associated AVWS for the management of invasive procedure.[8] This approach allowed to maintain target VWF:Act activity during the procedure. However, it cannot be used for prophylaxis regimen for practical reasons. Another way to get around this problem could be to use recombinant VWF. The only product currently on the market, vonicog α, is a recombinant VWF produced in a genetically engineered Chinese hamster ovary cell line.[9] Contrary to pdVWF, vonicog α is produced in the absence of the VWF-cleaving protease ADAMTS13 and contains all of the VWF multimers present in normal plasma, but also the ultra-large fraction (HMW) that is physiologically present only in endothelial cells and platelets. We made the hypothesis that the presence of these HMW would extend the half-life of VWF even in case of accelerated clearance.

Indeed, like Höpting et al, we have observed some biological response to vonicog α with VWF:Ag and FVIII levels doubling from baseline.[5] This treatment allowed a progressive control of the hemorrhagic symptomatology. Biological and clinical responses improved over time. This enabled us to maintain sufficient levels of Willebrand factor with fewer injections. Other factors such as ibrutinib treatment of the causative disease or anemia correction likely had some effects. However, in our case, the insufficient response to ibrutinib treatment and the persistence of major risk factors of bleeding led us to continue treatment with rVWF while progressively evolving toward a prophylactic regimen.

In conclusion, rVWF represents a potential therapeutic option in patients with AVWS for both the treatment of

 

bleeding episode and their prevention. However, additional data are needed to confirm these observations.

### Authors' Contributions

A.B. and C.L-B. drafted the case report. All authors reviewed and approved the final manuscript for publication.

### Conflicts of Interest

A.B. has received financial support from BMS, Takeda, Sobi, and LFB for registration fees and accommodation for scientific congress. S.C. has received financial support from CSL Behring for registration fees and accommodation for scientific congress. O.L. has received financial supports from MSD, BMS, AbbVie, and Boehringer for registration fees, education, and consultancy fees. C.L-B. has received financial supports from CSL Behring, Sobi, Novo Nordisk, Takeda, Octapharma, and LFB for registration fees and education fees. N.C. declares no conflict of interest.

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