



Efficacy of venetoclax-obinutuzumab treatment in achieving remission of acquired von Willebrand syndrome in chronic lymphocytic leukemia

Francesca Morelli¹ · Silvia Linari² · Chiara Maria Rapolla¹ · Monica Attanasio² · Francesca Salvianti² · Alessandro Sanna³

Received: 24 August 2025 / Accepted: 5 February 2026 / Published online: 14 March 2026
© The Author(s) 2026

Abstract

Venetoclax-obinutuzumab therapy successfully induced remission of acquired von Willebrand syndrome (AVWS) in a 72-year-old patient with chronic lymphocytic leukemia (CLL). Initially diagnosed with CLL, the patient later experienced severe bleeding due to AVWS, as evidenced by reduced factor VIII (FVIII) and von Willebrand factor (VWF) levels. Despite initial treatment with VWF/FVIII concentrates and tranexamic acid, persistent bleeding prompted the initiation of venetoclax-obinutuzumab. This regimen resulted in normalization of coagulation parameters and undetectable minimal residual disease, indicating effective CLL control and subsequent AVWS remission. This case highlights the potential of targeted CLL therapies in the management of rare associated hematologic complications.

Keywords Acquired von willebrand syndrome · Chronic lymphocytic leukemia · Venetoclax-obinutuzumab

Introduction

Chronic lymphocytic leukemia (CLL) is a hematological malignancy characterized by the clonal proliferation of mature B lymphocytes. While autoimmune complications like autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) are relatively common in CLL (AIHA 10–25%; ITP 5–10%) [1], the development of acquired von Willebrand syndrome (AVWS) is rarer (< 1%) [2–4]. AVWS arises due to various mechanisms, including accelerated removal of von Willebrand factor (VWF) from circulation, its adsorption onto malignant cells, degradation

by proteases, or the production of specific antibodies that inhibit VWF function [5]. Lymphoproliferative diseases are the most common hematological conditions associated with AVWS, with a higher prevalence in multiple myeloma and Waldenström macroglobulinemia, and a lower frequency in CLL [5, 6].

The management of AVWS in the context of CLL is challenging. Desmopressin, with or without FVIII/VWF concentrate, offers immediate but short-lived relief for bleeding episodes [7]. However, achieving durable remission hinges on treating the main cause – the CLL itself.

In the literature, there are sporadic cases of remission of AVWS secondary to treatment of the underlying disease: in particular, in one case remission was achieved with the combination of chlorambucil and the anti-CD20 monoclonal antibody obinutuzumab [8], in another the patient reestablished normal hemostasis after achieving a complete response after therapy with venetoclax and rituximab [4], while only sporadically this syndrome was treated with allogeneic hematopoietic stem cell transplantation [9].

✉ Alessandro Sanna
sannaa@aou-careggi.toscana.it

¹ Department of Hematology, University of Florence, Florence, Italy

² Center for Bleeding Disorders and Coagulation, Careggi University Hospital, Firenze, Italy

³ Department of Hematology, Careggi University Hospital, Largo Brambilla 3, Firenze 50134, Italy

Case presentation

In April 2022, a 72-years-old man was evaluated for lymphocytosis on peripheral blood with associated enlarged lymph nodes in the neck, axilla, and in the inguinal region, without hepatosplenomegaly.

After a peripheral blood smear showing an increase of mature-appearing lymphocytes and Gumprechts' shadows, we confirmed our suspicion of CLL RAI/Binet I/A stage performing a peripheral blood immunophenotype showing a population of mature B-lymphocytes ($5.97 \times 10^9/L$) with the following profile: CD19+, CD20-/+, CD22-/+, FMC7-, CD79b+, CD5+, CD23+, CD200+, CD38-/+(20%), CD43+, CD45+, and clonal surface Kappa light chains with weak expression intensity. The patient was then started on periodic watch-and-wait visits.

One year after the CLL diagnosis, the patient underwent orthopedic surgery to remove a Dupuytren's cyst from his left hand. Despite normal INR, activated prothrombin time (aPTT), and platelet count, surgery was complicated by massive bleeding. Platelet aggregation studies with ADP, collagen, arachidonic acid, thrombin, epinephrine were normal, while reduced ristocetin-induced platelet aggregation (22%, n.v. 68–100) was observed. Factor VII activity was normal (57 U/dL, n.v. 50–130), while factor VIII (FVIII) activity was reduced (28 U/dL, n.v. 50–150). Von Willebrand factor antigen (VWF: Ag) levels were also reduced (14.7U/dL, n.v. 60–160), along with VWF activity (5U/dL, n.v. 60–240) and collagen binding assay for VWF (VWF: CBA) (3 U/dL, n.v. 50–150). Additionally, plasma VWF multimer analysis revealed a reduction in high and intermediate weight multimers. Previous bleeding history was negative. The patient had no monoclonal components.

Suspecting AVWS secondary to CLL, inhibitors and genetic testing were also pursued.

While awaiting results, the patient was admitted to the ER for hematochezia resulting in anemia and he was treated with the intermediate-purity VWF/FVIII concentrate Talate (Takeda Manufacturing, Austria AG) at a dosage of 50 U/kg, with an improvement in FVIII and VWF plasma levels. As often described, the inhibitors against VWF were negative and genetic analysis of VWF identified a likely benign variant (c.6187 C > T, p.Pro2063Ser), supporting the hypothesis of secondary von Willebrand disease (VWD) (<https://erepo.clinicalgenome.org/evrepo/ui/classification/3e1c6372-35ab-4c65-8f6a-476e7c6e0a3b>). Anyway, while benign/likely benign variants are not causative of hereditary VWD, it cannot be completely excluded that this variant may have modestly influenced VWF homeostasis in the context of active CLL.

During hospitalization, a daily treatment with Talate (50U/kg) and tranexamic acid (TA) at a dosage of 25 mg/kg every 8 h was administered. Given the secondary nature of VWD and the persistence of hematochezia causing anemia despite replacement therapy, 12-months fixed treatment for CLL was initiated with venetoclax (AbbVie, Inc, North Chicago USA) and obinutuzumab (Roche, Basel CH). Obinutuzumab was administered intravenously for 6 cycles, starting with 100 mg on day 1 and 900 mg on day 2 of cycle 1, followed by 1000 mg on day 8 and 1000 mg on day 15. For cycles 2 through 6, 1000 mg was administered on day 1 of each cycle. The daily oral venetoclax regimen began on day 22 of cycle 1, starting with a 5-week dose ramp-up (20 mg, 50 mg, 100 mg, and 200 mg for 1 week each, then 400 mg daily for 1 week), and continued at 400 mg daily until the completion of cycle 12.

The biological evaluation of the disease was performed prior to treatment initiation and showed unmutated IGHV status, normal FISH and TP53 wild type.

After the first dose of obinutuzumab, a decrease in the white blood cell counts was observed, the patient experienced an episode of rectorrhagia, therefore both Talate and tranexamic acid were continued with daily monitoring of FVIII, VWF activity and VWF: Ag to assess for possible further changes in hemostatic therapy as soon as a response to CLL treatment was highlighted. (Table 1: coagulation labs before and during treatment).

The patient was discharged after starting venetoclax ramp-up and continued outpatient follow-up, showing normalization of FVIII, VWF: Ag, and VWF activity after completing the venetoclax ramp-up and obinutuzumab infusions (Table 1).

From June 16th, Talate and tranexamic acid were discontinued, and FVIII and VWF values remained within the normal range thereafter.

After the fixed-duration period of one year of treatment, minimal residual disease (MRD) on peripheral blood was performed, showing an undetectable cytofluorimetric MRD (Table 1).

Discussion

The management of CLL has evolved significantly over the past decade with the introduction of novel targeted therapies. Venetoclax, a selective B-cell lymphoma-2 (BCL-2) inhibitor, in combination with obinutuzumab, a type II anti-CD20 monoclonal antibody, has emerged as a highly effective regimen for CLL treatment. This combination has demonstrated superior efficacy compared to chemoimmunotherapy,

Table 1 Coagulation labs before and during treatment

Baseline (pre-hematochezia)	Leukocytes ($\times 10^9/L$)	Lymphocytes ($\times 10^9/L$)	aPTT sec (25–37)	FVIII % (50–150)	VWF: AG % (60–160)	VWF activity % (60–240)	CLL status
	66.10	57.97	35.2	28	14.7	5	Watch and wait
Post I Talate infusion	65.6	n.a	26.3	70.3	49	26.7	Watch and wait
Pre VO	61.7	n.a	24.9	59.9	47.5	24	Watch and wait
Post 1° O dose 100 mg	28.6	n.a	29.3	98.6	85.3	43.1	SD
Post 2° O	8.12	n.a	30.4	39.1	36.5	13.5	SD
Post 3° O	18.3	n.a	n.a	82.8	43	19.5	SD
Pre-V start	4.88	n.a	n.a	57	20.8	4.3	SD
Post V 20 mg	5.11	3.04	n.a	208	18	3.4	PR
Post V 400 mg	3	1.54	37	76.9	61	51.2	cCR
Last O	4.54	1.48	25	117.8	141	162	cCR
End of treatment	5.31	2.22	26	171	158	172	CR uMRD

aPTT: activated partial thromboplastin time; FVIII: factor VIII; VWF: AG: vonWillebrand factor Antigen; VO: venetoclax obinutuzumab; O: obinutuzumab; V: venetoclax; SD: stable disease; PR: partial response; cCR: clinical CR; CR: complete response; uMRD: undetectable Minimal residual disease; n.a: not available

particularly in patients with comorbidities or those harboring high-risk genetic features [10].

One of the remarkable achievements of venetoclax-obinutuzumab therapy is the attainment of minimal residual disease (MRD) negativity, translating into deep and durable remission. MRD negativity has become a key goal in CLL management, as it correlates with improved progression-free survival and potentially offers the prospect of treatment-free intervals. In our case, the patient achieved MRD negativity in peripheral blood after a fixed-duration treatment period, underscoring the efficacy of this regimen.

AVWS represents a rare but clinically significant complication of CLL, often posing diagnostic and therapeutic challenges. The pathogenesis of AVWS in CLL involves various mechanisms, including accelerated clearance or proteolytic degradation of von Willebrand factor, the development of VWF-inhibiting antibodies, or adsorption onto malignant cells.

Successful treatment of CLL and attainment of MRD negativity may induce remission of AVWS through several potential mechanisms. In particular, CLL-directed therapies such as venetoclax-obinutuzumab, target the underlying lymphoproliferative process, reducing the burden of malignant B cells and associated dysregulated immune responses. This could mitigate the aberrant production of VWF-Ig complexes and restore VWF homeostasis.

This case underscores the rarity of AVWS in the setting of CLL and highlights the limited literature on this topic. While autoimmune complications such as autoimmune hemolytic anemia and immune thrombocytopenia are relatively common in CLL and with a well-known treatment strategy, AVWS remains a limited-reported entity.

Conclusion

In this case report, we presented a 72-year-old man with CLL who developed AVWS during the history of his hematological disease. Despite initial challenges in diagnosis and management, the patient achieved remission of AVWS with venetoclax-obinutuzumab therapy targeted at CLL.

The successful outcome observed in this case underscores the efficacy of venetoclax-obinutuzumab in achieving deep and durable remission of CLL, as evidenced by the attainment of undetectable MRD.

The mechanisms underlying the resolution of AVWS following CLL-directed therapy are multifactorial: effective CLL treatment likely reduces the burden of malignant B cells and associated dysregulated immune responses restoring VWF homeostasis.

This case emphasizes the importance of identifying and managing rare blood-related complications like AVWS in the context of CLL. By documenting successful treatment approaches with new targeted therapies like venetoclax-obinutuzumab, we deepen our understanding of the complex relationship between blood cancers and clotting disorders, offering valuable insights for future clinical practice and research efforts.

Author contributions Francesca Morelli and Silvia Linari were responsible for writing the paper. The conception and design of the work were developed by Francesca Morelli and Alessandro Sanna. Supervision was provided by Alessandro Sanna. All authors, including Francesca Morelli, Silvia Linari, Chiara Maria Rapolla, Monica Attanasio, Francesca Salvianti, and Alessandro Sanna, reviewed and approved the final manuscript and gave final approval of the version to be published.

Funding None.

Data availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Ethics approval Not required due to the nature of the case report itself.

Patient consent Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

Permission to reproduce material from other sources Not applicable.

Competing interests The authors declare no competing interests.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

- Gordon MJ, Ferrajoli A (2022) Unusual complications in the management of chronic lymphocytic leukemia. *Am J Hematol* 97(S2):S26–S34. <https://doi.org/10.1002/AJH.26585>
- Kumar S, Pruthi RK, Nichols WL (2003) Acquired von willebrand's syndrome: a single institution experience. *Am J Hematol* 72(4):243–247. <https://doi.org/10.1002/AJH.10298>
- Jung M, Rice L (2011) Unusual autoimmune nonhematologic complications in chronic lymphocytic leukemia. *Clin Lymphoma Myeloma Leuk* 11 Suppl 1(SUPPL.1). <https://doi.org/10.1016/J.CLML.2011.02.005>
- Innocenti I, Morelli F, Autore F et al (2019) Remission of acquired von Willebrand syndrome in a patient with chronic lymphocytic leukemia treated with venetoclax. *Leuk Lymphoma* 60(12):3078–3080. <https://doi.org/10.1080/10428194.2019.1612063>
- Tiede A, Susen S, Lisman T (2024) Acquired bleeding disorders. *Haemophilia* 30:29–38. <https://doi.org/10.1111/HAE.14995>
- Federici A, Budde U, Castaman G, Rand J, Tiede A (2013) Current diagnostic and therapeutic approaches to patients with acquired von Willebrand syndrome: A 2013 update. *Semin Thromb Hemost* 39(2):191–201. <https://doi.org/10.1055/S-0033-1334867/ID/JR01958-16/BIB>
- Biguzzi E, Siboni SM, Peyvandi F (2018) Acquired von Willebrand syndrome and response to Desmopressin. *Haemophilia* 24(1):e25–e28. <https://doi.org/10.1111/HAE.13382>
- Khalife R, Aw A, Duffett L et al (2021) To treat or not? Remission induction of acquired von Willebrand syndrome secondary to chronic lymphocytic leukemia: A case report. *Clin Lymphoma Myeloma Leuk* 21(6):e493–e496. <https://doi.org/10.1016/J.CLML.2021.01.007>
- Hegerova L, He F, Zantek ND, Vercellotti GM, Holtan SG, Reding MT (2019) Reversal of acquired von Willebrand syndrome with allogeneic stem cell transplant for chronic lymphocytic leukemia. *Blood Cells Mol Dis* 77:109–112. <https://doi.org/10.1016/J.BCMD.2019.04.009>
- Al-Sawaf O, Robrecht S, Zhang C, Olivieri S, Chang YM, Fink AM, Tausch E, Schneider C, Ritgen M, Kreuzer KA, Sivchev L, Niemann CU, Schwarzer A, Loscertales J, Weinkove R, Strumberg D, Kilfoyle A, Manzoor BS, Jawaidd D, Emechebe N, Devine J, Boyer M, Runkel ED, Eichhorst B, Stilgenbauer S, Jiang Y, Hallek M, Fischer K (2024) Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 6-year results of the randomized phase 3 CLL14 study. *Blood* 144(18):1924–1935. <https://doi.org/10.1182/blood.2024024631> PMID: 39082668; PMCID: PMC11551846

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.