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LETTER TO THE EDITOR

Inhibitor eradication in refractory acquired hemophilia with lenalidomide

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Dear Editor,

Acquired hemophilia A (AHA) is a very rare disease caused by antibodies against factor VIII (FVIII). Standard treatment consists of steroids, cyclophosphamide, and rituximab. However, only 42–70% of all patients achieve long-term remission after first-line treatment [1, 2]. The optimal treatment of refractory AHA is still controversial.

We report on a 66-year-old male patient diagnosed with AHA after spontaneous spinal bleeding resulting in paraplegia. Initial FVIII activity was < 1% and the inhibitor titer 700 Bethesda units (BU). Before the diagnosis of AHA, he was healthy and not taking any medication. Diagnostic workup showed 0.75% atypical B cells in the bone marrow but no cytologic abnormalities and a regular male karyotype. Immunofixation was weakly positive for IgG kappa but serum electrophoresis and free light chains were normal. CT scan did not reveal any sign of an underlying disease and there was no evidence for a rheumatologic disorder.

Inhibitor eradication was initiated with prednisolone, followed by cyclophosphamide and a single dose of rituximab resulting in complete remission according to the GTH-AHA study [1]. The patient relapsed 6 months later but responded to prednisolone pulse therapy. However, he had a second relapse another 10 months later. Bone marrow cytology showed 18% plasma cells with a regular kappa to lambda distribution and negative clonality analysis and without evidence of atypical B cells. Immunofixation was still positive. The patient was treated with four cycles of rituximab followed by three cycles of 750 mg/m^2 cyclophosphamide i.v. without sustained remission.

Due to recurrent life-threatening bleeds, therapy was switched to a combination of bendamustine, prednisolone and bortezomib (BPV). FVIII activity increased to 40% but BPV had to be discontinued after three cycles due to infectious complications. After discontinuation of BPV, FVIII activity decreased to 9.9%. Thus, treatment was switched to bortezomib monotherapy leading to complete remission. Unfortunately, bortezomib had to be discontinued due to neuropathy, leading to the next relapse 1 month later. Alternative options for immunosuppression were considered and azathioprine at a dose of 50 mg twice daily was started. The patient responded to a concomitantly administered prednisolone pulse but azathioprine did not show any effect. As azathioprine was ineffective, other options for immunosuppression like mycophenolate mofetil or calcineurin inhibitors were expected to be ineffective too.

Finally, lenalidomide in the lowest available dose of 5 mg daily for 21 days of a 28-day cycle was started and a basic low-dose prednisolone therapy of 7.5 mg was kept. The patient responded with an increase in FVIII activity to 30% after 4 cycles. Lenalidomide dose was reduced and finally discontinued due to a skin rash resulting in a decreasing FVIII activity to 2.6%. Lenalidomide was restarted at 10 mg daily after the skin rash had disappeared. The patient responded with a sustained complete remission after six cycles of lenalidomide as an ongoing treatment combined with

On behalf of my co-authors, I state that the material is original research, has not been previously published, and has not been submitted for publication elsewhere while under consideration

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5 mg prednisolone without side effects. The inhibitor titer remained negative after initiation of BPV in the Bethesda method and was only weakly positive in the Nijmegen-modified method when FVIII activity dropped below 10% (Fig. 1).

This is, to our knowledge, the first report demonstrating the efficacy of lenalidomide as a therapeutic option in a patient with AHA. Bortezomib was already used in AHA related to [3], as well as not related to multiple myeloma [4]. Bortezomib induces apoptosis in antibody-secreting cells, reduces proliferation of activated B cells and modulates T cell response via an increase in regulatory T cells [5]. In a recent case series of patients with autoimmune hematologic diseases receiving bortezomib as salvage therapy, responding patients had an immediate improvement after initiation of the drug [6]. However, some patients experienced early relapse after discontinuation of bortezomib similar to our patient. Since all patients were pretreated with rituximab, bortezomib-induced depletion of plasma cells apart from the additive effect to rituximab on $CD20^+$ B cells might be the key pathophysiologic explanation for the response of these autoimmune diseases to bortezomib. This explanation is supported by observations from patients with systemic lupus erythematosus (SLE) showing a quick response to bortezomib going along with depletion in peripheral blood and bone marrow plasma cells but not $CD20^+$ B cells [7]. Whether the additive effects of proteasome inhibition on Toll-like receptor induced IFN-α production as shown in this case series and in a murine model of SLE [8] can be adapted to patients with autoimmune hematologic diseases is still unknown.

Lenalidomide is a well-established treatment option in multiple myeloma, myelodysplastic syndrome with 5q deletion, and lymphoproliferative diseases. The mechanism of action of lenalidomide is not completely understood. Beside its cytotoxic effects on malignant plasma cells, it has immune-stimulating effects on effector T and NK cells and leads to an increase in regulatory T cells [9–11]. Preliminary data show its efficacy in the treatment of autoimmune diseases [12, 13] while others reported an association of lenalidomide with the induction of autoimmune diseases in patients treated for hematologic diseases [14, 15] and even the induction of AHA in a patient with multiple myeloma (MM) [16]. These contradictory findings might be explained with the fact that $CD4^+CD25^+$ regulatory T cells are upregulated [17] and dysfunctional [18] in patients with MM leading to a differential response to lenalidomide. Other subsets of regulatory T cells such as $CD8^+CD28^-$ T cells which can induce an imbalance between TH1 and TH2 cytokines [19] might play an additional role. These cells are known to be overexpressed in various types of cancer and defective in autoimmune diseases and can be decreased by lenalidomide as shown in an in vitro model in healthy donors and MM patients [9].

However, besides the postulated immunomodulatory effect of bortezomib and lenalidomide, it is most likely that the depletion of plasma cells, which is not mediated by rituximab, is the main mode of action in this patient.

It remains speculative whether the patient is suffering from a smoldering malignant hematologic or autoimmune disorder. Nevertheless, the response to bortezomib and lenalidomide, especially the quick response to the increased dose of lenalidomide, shows the potential of both drugs in patients with refractory AHA.

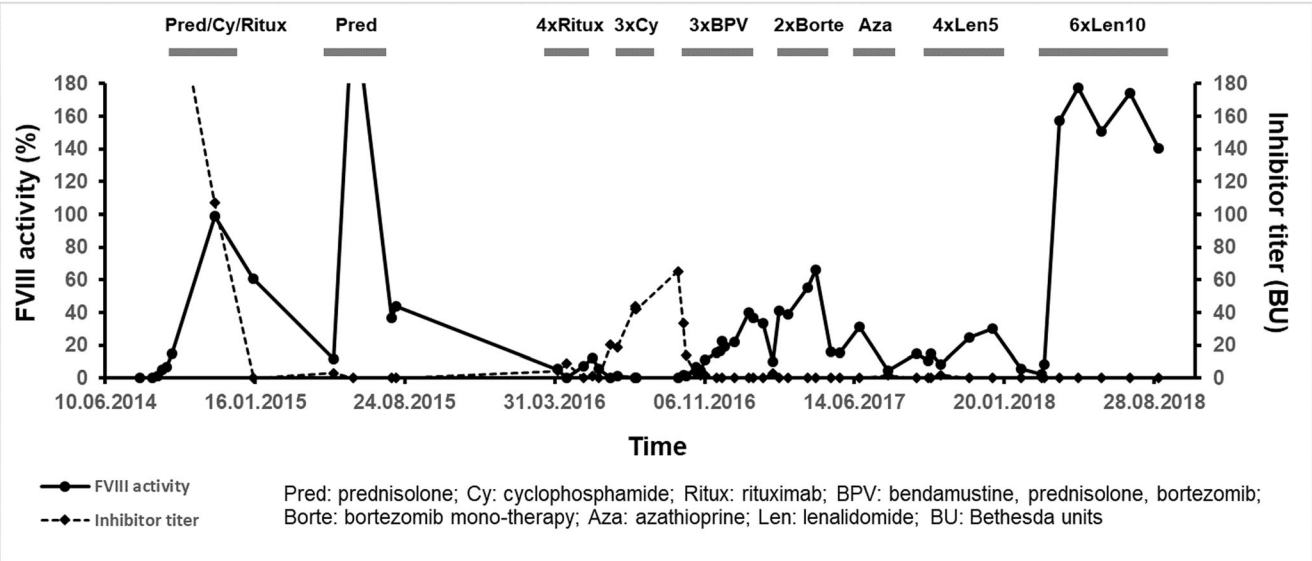

Fig. 1 Factor VIII activity, inhibitor titer, and applied therapies over time

Compliance with ethical standards

Conflict of interest The authors declared that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from the patient for being included in the study.

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References

1. Tiede A, Klamroth R, Scharf RE, Trappe RU, Holstein K, Huth-Kuhne A, Gottstein S, Geisen U, Schenk J, Scholz U, Schilling K, Neumeister P, Miesbach W, Manner D, Greil R, von Auer C, Krause M, Leimkuhler K, Kalus U, Blumtritt JM, Werwitzke S, Budde E, Koch A, Knobl P (2015) Prognostic factors for remission of and survival in acquired hemophilia A (AHA). Results from the GTH-AH 01/2010 study. Blood 125(7):1091–1097. https://doi.org/10.1182/blood-2014-07-587089
2. Collins P, Baudo F, Knoebl P, Levesque H, Nemes L, Pellegrini F, Marco P, Tengborn L, Huth-Kuhne A, on behalf of the EACH2 registry collaborators (2012) Immunosuppression for acquired hemophilia A. Results from the European Acquired Haemophilia Registry (EACH2). Blood 120(1):47–55. https://doi.org/10.1182/blood-2012-02-409185
3. Brás GP, Pinto RJSM, Carvalho MMMC, Fernandes S, Andrade J, Guimarães J (2017) Bortezomib. Potential key role in the treatment of multiple myeloma-related acquired hemophilia a. Semin Thromb Hemost 43(1):109–112. https://doi.org/10.1055/s-0036-1597648
4. McFadyen JD, Tran H, Kaplan ZS (2017) Factor VIII inhibitor eradication with bortezomib in acquired haemophilia A. Br J Haematol 178(6):986–987. https://doi.org/10.1111/bjh.14185
5. Pellom ST, Dudimah DF, Thounaojam MC et al (2015) Modulatory effects of bortezomib on host immune cell functions. Immunotherapy 7(9):1011–1022. https://doi.org/10.2217/imt.15.66
6. Ratnasingam S, Walker PA, Tran H, Kaplan ZS, McFadyen JD, Tran H, Teh TC, Fleming S, Catalano JV, Chunilal SD, Johnston A, Opat SS, Shortt J (2016) Bortezomib-based antibody depletion for refractory autoimmune hematological diseases. Blood Adv 1(1):31–35. https://doi.org/10.1182/bloodadvances.2016001412
7. Alexander T, Sarfert R, Klotsche J, Kühl AA, Rubbert-Roth A, Lorenz HM, Rech J, Hoyer BF, Cheng Q, Waka A, Taddeo A, Wiesener M, Schett G, Burmester GR, Radbruch A, Hiepe F, Voll RE (2015) The proteasome inhibitior bortezomib depletes plasma cells and ameliorates clinical manifestations of refractory systemic lupus erythematosus. Ann Rheum Dis 74(7):1474–1478. https://doi.org/10.1136/annrheumdis-2014-206016
8. Ichikawa HT, Conley T, Muchamuel T, Jiang J, Lee S, Owen T, Barnard J, Nevarez S, Goldman BI, Kirk CJ, Looney RJ, Anolik JH (2012) Beneficial effect of novel proteasome inhibitors in murine lupus via dual inhibition of type I interferon and autoantibody-secreting cells. Arthritis Rheum 64(2):493–503. https://doi.org/10.1002/art.33333
9. Neuber B, Dai J, Waraich WA, Awwad MHS, Engelhardt M, Schmitt M, Medenhoff S, Witzens-Harig M, Ho AD, Goldschmidt H, Hundemer M (2017) Lenalidomide overcomes the immunosuppression of regulatory CD8+CD28- T-cells. Oncotarget 8(58):98200–98214. https://doi.org/10.18632/oncotarget.21516
10. Zhang L, Bi E, Hong S, Qian J, Zheng C, Wang M, Yi Q (2015) $CD4^+$ T cells play a crucial role for lenalidomide in vivo anti-tumor activity in murine multiple myeloma. Oncotarget 6(34):36032–36040. https://doi.org/10.18632/oncotarget.5506
11. Balaian E, Schuster C, Schönefeldt C, Germing U, Haase D, Tuve S, Ordemann R, Ehninger G, Bornhäuser M, Oelschlaegel U, Mohr B, von Bonin M, Platzbecker U, Wermke M (2016) Selective expansion of regulatory T cells during lenalidomide treatment of myelodysplastic syndrome with isolated deletion 5q. Ann Hematol 95(11):1805–1810. https://doi.org/10.1007/s00277-016-2775-y
12. Lopez-Millan B, La Diaz de Guardia R, Roca-Ho H, García-Herrero CM, Lavoie JR, Rosu-Myles M, Gonzalez-Rey E, O'Valle F, Criado G, Delgado M, Menendez P (2017) Therapeutic effect of the immunomodulatory drug lenalidomide, but not pomalidomide, in experimental models of rheumatoid arthritis and inflammatory bowel disease. Exp Mol Med 49(2):e290. https://doi.org/10.1038/emm.2016.143
13. Wu EY, Schanberg LE, Wershba EC, Rabinovich CE (2017) Lenalidomide for refractory cutaneous manifestations of pediatric systemic lupus erythematosus. Lupus 26(6):646–649. https://doi.org/10.1177/0961203316676377
14. Montefusco V, Galli M, Spina F, Stefanoni P, Mussetti A, Perrone G, de Philippis C, Dalto S, Maura F, Bonini C, Rezzonico F, Pennisi M, Roncari L, Soldarini M, Dodero A, Farina L, Cocito F, Caprioli C, Corradini P (2014) Autoimmune diseases during treatment with immunomodulatory drugs in multiple myeloma. Selective occurrence after lenalidomide. Leuk Lymphoma 55(9):2032–2037. https://doi.org/10.3109/10428194.2014.914203
15. Loree JM, Cai E, Sheffield BS, Dutz JP, Villa D, Shepherd LE, Connors JM, Sehn LH, Savage KJ (2017) Leukocytoclastic vasculitis following lenalidomide during the treatment of follicular lymphoma. Leuk Lymphoma 58(3):711–714. https://doi.org/10.1080/10428194.2016.1204657
16. Saburi M, Ohtsuka E, Itani K, Nagamatsu K, Ikebe T, Miyazaki Y, Ogata M, Saburi Y (2015) Development of acquired hemophilia a during treatment of multiple myeloma with lenalidomide. Rinsho Ketsueki 56(5):496–500. https://doi.org/10.11406/rinketsu.56.496
17. Braga WMT, da Silva BR, de Carvalho AC et al (2014) FOXP3 and CTLA4 overexpression in multiple myeloma bone marrow as a sign of accumulation of CD4(+) T regulatory cells. Cancer Immunol Immunother 63(11):1189–1197. https://doi.org/10.1007/s00262-014-1589-9
18. Feyler S, von Lilienfeld-Toal M, Jarmin S, Marles L, Rawstron A, Ashcroft AJ, Owen RG, Selby PJ, Cook G (2009) CD4(+)CD25(+)FoxP3(+) regulatory T cells are increased whilst CD3(+)CD4(−)CD8(−)alphabetaTCR(+) double negative T cells are decreased in the peripheral blood of patients with multiple myeloma which correlates with disease burden. Br J Haematol 144(5):686–695. https://doi.org/10.1111/j.1365-2141.2008.07530.x
19. Saurwein-Teissl M, Lung TL, Marx F, Gschosser C, Asch E, Blasko I, Parson W, Bock G, Schonitzer D, Trannoy E, Grubeck-Loebenstein B (2002) Lack of antibody production following immunization in old age. Association with CD8+CD28- T cell clonal expansions and an imbalance in the production of Th1 and Th2 cytokines. J Immunol 168(11):5893–5899. https://doi.org/10.4049/jimmunol.168.11.5893