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Single Case

Vedolizumab Treatment for Ulcerative Colitis in an Elderly Multimorbid Patient with Hemophilia A

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Keywords
Ulcerative colitis · Hemophilia A · Vedolizumab · Primary sclerosing cholangitis

Abstract
The treatment of inflammatory bowel diseases (IBD) can be challenging, especially in elderly multimorbid patients. Since incidence and prevalence rates of IBD are rising steadily, treatment of older patients with relevant and also rare comorbidities will be of increasing relevancy for caregivers. Here we report on a 74-year-old multimorbid patient with severe ulcerative colitis (UC) and hemophilia A. Because of the chronic active disease, therapy with a tumor necrosis factor-α inhibitor was started. He suffered from a severe infectious complication (pneumonia) under therapy with infliximab. The therapy was changed to vedolizumab, with which the patient stayed in long-term clinical and endoscopic remission. Because the patient had a non-ST-segment elevation myocardial infarction in April 2016, he received dual platelet inhibitor therapy with aspirin and clopidogrel. Because of consecutive aspirin intolerance, the therapy was changed to clopidogrel monotherapy. Although the UC was treated appropriately with vedolizumab and the patient was in endoscopic mucosal remission, recurrent bleeding episodes from multiple inflammatory pseudopolyps occurred. The bleeding episodes resolved quickly after immediate treatment with factor VIII (Kogenate®). In conclusion, we describe the first patient in the literature with UC and hemophilia A who stayed in long-term remission under therapy with vedolizumab. From our point of view, vedolizumab can be

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safely administered in the setting of UC and hemophilia A. Antiplatelet drugs which inhibit primary hemostasis must be used with caution in this setting. Bleeding episodes can be treated safely and effectively with factor VIII (Kogenate®).

Background

Inflammatory bowel diseases (IBD) mainly consist of Crohn's disease and ulcerative colitis (UC) and are chronic inflammatory disorders of the alimentary tract [1–3]. Patients with UC suffer from bloody diarrhea, abdominal pain, weight loss, and fatigue. Standard treatment of UC consists of aminosalicylates, purine antimetabolites, steroids, tumor necrosis factor (TNF) antibodies, and antibodies blocking lymphocyte trafficking in the gut, i.e., vedolizumab [4]. Compared to TNF antibodies, which can cause serious infectious complications (e.g., tuberculosis [5, 6]), vedolizumab seems to have a more favorable risk profile [7, 8]. Vedolizumab is an $\alpha_4\beta_7$ humanized antibody inhibiting the adhesion of gut-homing T lymphocytes to mucosal vascular addressin cell adhesion molecule 1 [9, 10]. This approach leads to a selective downregulation of inflammation in the gut, while the systemic immune system is not impaired [11, 12]. Therefore, vedolizumab has become an important treatment option for IBD patients at a higher risk of infectious complications, especially elderly patients.

Hemophilia A is a rare bleeding disorder caused by mutations in the factor VIII gene [13], which is part of the intrinsic pathway of blood coagulation. The prevalence of hemophilia A is 1 in 5,000 male live births [13, 14]. The clinical efficacy of treatment with recombinant factor VIII was first described in 1989 [15]. Since treatment options have improved, hemophilia patients now have an increased life expectancy approaching that of the general population [16–18]. Therefore, relevant comorbidities play a substantial role for their caregivers [19, 20]. Especially cardiovascular diseases are important medical conditions in patients with hemophilia A [21, 22].

In this case report, we describe a 74-year-old male with UC and a mild form of hemophilia A. To the best of our knowledge, this is the first patient treated with vedolizumab for UC in the clinical setting of hemophilia A. From our point of view, since the patient is in long-term clinical and endoscopic remission, vedolizumab can be safely administered in this rare clinical scenario.

Case Presentation

We report on a 74-year-old male Caucasian patient who had been diagnosed with UC in 2003. The initial manifestation of the disease was pancolitis. After having been diagnosed, he had a chronic active disease with 2–4 flares a year. His initial therapy consisted of aminosalicylates and 6-mercaptopurine, and acute flares were treated with steroids. In 2013, 6-mercaptopurine was stopped because of its inefficiency. A colonoscopy was performed in August 2013, which showed severe inflammation from the right colonic flexure to the rectum, as well as multiple inflammatory pseudopolyps (Fig. 1a). Treatment with infliximab was initiated in September 2014. Soon after the first dose, the patient was in clinical remission. However, about 8 weeks later, in November 2014, he developed severe pneumonia with *Staphylococcus haemolyticus* and additionally an allergic reaction to the next infliximab infusion. Therefore, the therapy with infliximab was stopped. In January 2015, therapy with

vedolizumab was started. A colonoscopy was performed in August 2015, which showed endoscopic remission; but again, multiple inflammatory pseudopolyps could be detected all over the colon (Fig. 1b). Until now (May 2017), the patient has stayed in long-term clinical remission without steroids under vedolizumab without significant flares.

Other Preexisting Medical Conditions

Besides severe UC, the patient has the following clinical comorbidities: mild hemophilia A, and coronary artery disease, with a consecutive non-ST-segment elevation myocardial infarction in April 2016 which required the application of two bare metal stents and one drug-eluting stent. The patient had been placed on dual platelet aggregation inhibition with aspirin and clopidogrel for 1 year. Because of aspirin intolerance, the dual platelet aggregation inhibition was changed to a monotherapy with clopidogrel. Additionally, the patient has arterial hypertension, diabetes mellitus type 2, adiposity, and primary sclerosing cholangitis.

Although the patient was in clinical and also endoscopic remission under treatment with vedolizumab, he suffered from lower gastrointestinal (GI) bleeding about once a year due to his hemophilia A; the bleeding episodes were more frequent after placement of the coronary artery stents. The lower GI bleeding was attributed to the multiple inflammatory pseudopolyps. An upper GI bleeding source could be ruled out by esophagogastroduodenoscopy. His normal factor VIII level was around 8%, which is usually classified as mild disease [14, 20]. The bleeding episodes could be treated by infusion with factor VIII (Kogenate®) without any complication. The bleeding usually resolved soon after administration of the factor VIII.

Discussion and Conclusions

This case has different relevant teaching points. First, vedolizumab can be safely administered for the treatment of UC to patients with hemophilia A. Our patient has stayed in long-term clinical and endoscopic remission after failure of different therapies (TNF-α antagonist and purine antimetabolites). To the best of our knowledge, this is the first case described in the literature where vedolizumab has been administered to a patient with hemophilia A. Since the prevalence of IBD is increasing steadily [23], patients with IBD and rare diseases like hemophilia A will possibly be more common, and safety issues will become an important issue in this patient cohort.

Second, lower GI bleeding episodes in hemophilia A and UC can be treated effectively with factor VIII concentrates. In our patient, the bleeding sources were most likely the multiple inflammatory pseudopolyps, since endoscopically the patient was in remission. However, due to his bleeding disorder and other relevant comorbidities, we did not perform an endoscopic resection of the countless inflammatory pseudopolyps. Since the patient comes to the hospital as soon as bleeding starts, factor VIII can be applied immediately. Another important issue is surveillance. Since our patient is also suffering from primary sclerosing cholangitis, yearly colonoscopies are needed according to German guidelines [24]. We performed colonoscopies in 2013 and 2015, and in between, a colonoscopy was performed in another hospital, where the coronary artery stents were placed. However, sampling of mucosal biopsies has to be weighed against a high risk of bleeding. In future, we are planning to perform chromoendoscopy. A colectomy was also discussed with the patient. However, he has been in endoscopic and clinical remission, has multiple comorbidities, and also refuses a surgical approach.

Third, in a patient with multiple relevant comorbidities (UC, hemophilia A, and coronary artery disease), drugs which might increase the risk of bleeding by inhibiting primary hemostasis must be administered with caution.

Since treatment of this patient involves many different medical disciplines, we think that an interdisciplinary approach is best suited for elderly hemophilia patients with different complex and rare comorbidities.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Disclosure Statement

All authors declare that they have no competing interests.

Author Contributions

All authors participated in preparation, reading, and approval of the manuscript. A.H. and H.S. were the attending physicians responsible for treatment of the UC. O.A. performed treatment of the hemophilia A.

References

1 Abraham C, Cho JH: Inflammatory bowel disease. N Engl J Med 2009;361:2066–2078.
2 Baumgart DC, Sandborn WJ: Crohn's disease. Lancet 2012;380:1590–1605.
3 Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ: Ulcerative colitis. Lancet 2012;380:1606–1619.
4 Cholapranee A, Hazlewood GS, Kaplan GG, Peyrin-Biroulet L, Ananthakrishnan AN: Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. Aliment Pharmacol Ther 2017;45:1291–1302.
5 Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, et al: Tuberculosis associated with infliximab, a tumor necrosis factor α-neutralizing agent. N Engl J Med 2001;345:1098–1104.
6 Ford AC, Peyrin-Biroulet L: Opportunistic infections with anti-tumor necrosis factor-α therapy in inflammatory bowel disease: meta-analysis of randomized controlled trials. Am J Gastroenterol 2013;108:1268–1276.
7 Feagan BG, Rubin DT, Danese S, Vermeire S, Abhyankar B, Sankoh S, et al: Efficacy of vedolizumab induction and maintenance therapy in patients with ulcerative colitis, regardless of prior exposure to tumor necrosis factor antagonists. Clin Gastroenterol Hepatol 2017;15:229–239.e5.
8 Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel J-F, Sandborn WJ, et al: Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369:699–710.
9 Soler D, Chapman T, Yang L-L, Wyant T, Egan R, Fedyk ER: The binding specificity and selective antagonism of vedolizumab, an anti-$\alpha_4\beta_7$ integrin therapeutic antibody in development for inflammatory bowel diseases. J Pharmacol Exp Ther 2009;330:864–875.
10 von Andrian UH, Engelhardt B: α_4 Integrins as therapeutic targets in autoimmune disease. N Engl J Med 2003;348:68–72.
11 Fedyk ER, Wyant T, Yang L-L, Csizmadia V, Burke K, Yang H, Kadambi VJ: Exclusive antagonism of the $\alpha_4\beta_7$ integrin by vedolizumab confirms the gut-selectivity of this pathway in primates. Inflamm Bowel Dis 2012;18:2107–2119.

12 Milch C, Wyant T, Xu J, Parikh A, Kent W, Fox I, Berger J: Vedolizumab, a monoclonal antibody to the gut homing $\alpha_4\beta_7$ integrin, does not affect cerebrospinal fluid T-lymphocyte immunophenotype. J Neuroimmunol 2013;264:123–126.

13 Mannucci PM, Tuddenham EG: The hemophilias – from royal genes to gene therapy. N Engl J Med 2001;344:1773–1779.

14 Bolton-Maggs PHB, Pasi KJ: Haemophilias A and B. Lancet 2003;361:1801–1809.

15 White GC 2nd, McMillan CW, Kingdon HS, Shoemaker CB: Use of recombinant antihemophilic factor in the treatment of two patients with classic hemophilia. N Engl J Med 1989;320:166–170.

16 Larsson SA: Life expectancy of Swedish haemophiliacs, 1831–1980. Br J Haematol 1985;59:593–602.

17 Walker IR, Julian JA: Causes of death in Canadians with haemophilia 1980–1995. Association of Hemophilia Clinic Directors of Canada. Haemophilia 1998;4:714–720.

18 Darby SC, Kan SW, Spooner RJ, Giangrande PLF, Hill FGH, Hay CRM, et al: Mortality rates, life expectancy, and causes of death in people with hemophilia A or B in the United Kingdom who were not infected with HIV. Blood 2007;110:815–825.

19 Mauser-Bunschoten EP, Fransen Van De Putte DE, Schutgens RE: Co-morbidity in the ageing haemophilia patient: the down side of increased life expectancy. Haemophilia 2009;15:853–863.

20 Franchini M, Tagliaferri A, Mannucci PM: The management of hemophilia in elderly patients. Clin Interv Aging 2007;2:361–368.

21 Coppola A, Tagliaferri A, Franchini M: The management of cardiovascular diseases in patients with hemophilia. Semin Thromb Hemost 2010;36:91–102.

22 Mannucci PM, Mauser-Bunschoten EP: Cardiovascular disease in haemophilia patients: a contemporary issue. Haemophilia 2010;16(suppl 3):58–66.

23 Molodecky NA, Soon IS, Rabi DM, Ghali WA, Ferris M, Chernoff G, et al: Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. Gastroenterology 2012;142:46–54.e42; quiz e30.

24 Dignass A, Preiss JC, Aust DE, Autschbach F, Ballauff A, Barretton G, et al: Aktualisierte Leitlinie zur Diagnostik und Therapie der Colitis ulcerosa 2011 – Ergebnisse einer Evidenzbasierten Konsensuskonferenz. Z Gastroenterol 2011;49:1276–1341.

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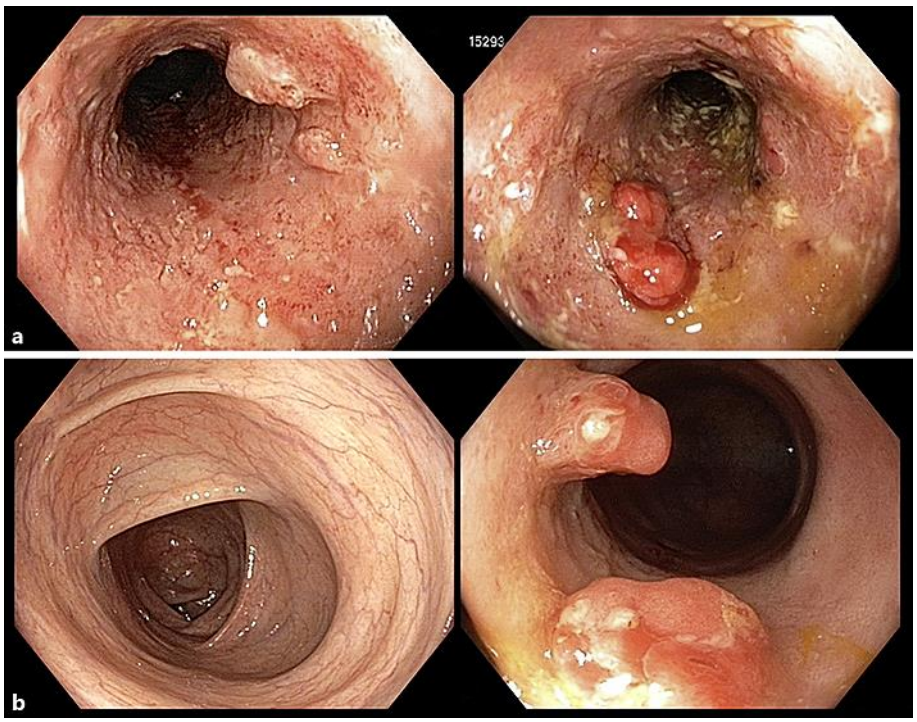

Fig. 1. Colonic mucosa before (**a**) and after (**b**) the administration of vedolizumab. Countless inflammatory pseudopolyps can be noticed throughout the colon. While before treatment with vedolizumab the Mayo score had been 2, under treatment with vedolizumab the Mayo score improved to 0–1.