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

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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 relevance 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
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 α4β7 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.

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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.