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CASE REPORT

Anti-integrin treatment as an effective alternative for a patient with ulcerative colitis

Ewa Antonina Biegańska[1], Karol Rokicki[1], Katarzyna Karolewska-Bochenek[2], Izabella Łazowska-Przeorek[2], Marcin Banasiuk[2]

[1]Student Research Association of Paediatric Emergency Medicine, Medical University of Warsaw, Warsaw, Poland
[2]Department of Paediatric Gastroenterology and Nutrition, Medical University of Warsaw, Warsaw, Poland

ABSTRACT

Paediatric ulcerative colitis (UC) has a tendency to run in an extensive manner, with frequent exacerbations. As a result, treatment of paediatric patients is a complex process demanding thorough evaluation, careful monitoring, and selection of appropriate medication. We present a case report of UC in an 11-year-old boy diagnosed at the age of 7 years. During 3 years of treatment many therapeutic methods were used, but none brought a long-lasting therapeutic effect. Due to exhaustion of available therapeutic options, off-label treatment with vedolizumab was introduced. Currently, in his 15th month of the therapy, the patient remains in remission. This case, in line with the available literature, indicates that there might be a need to include vedolizumab to the UC standard treatment regimens. Moreover, it should also be considered for inclusion in funding programs of national health insurance companies. It is of a crucial importance for patients because in some cases it remains the last treatment option.

KEY WORDS:
ulcerative colitis, vedolizumab, inflammatory bowel diseases, paediatric ulcerative colitis.

INTRODUCTION

Ulcerative colitis (UC) is estimated to have an incidence of 9 to 20 cases per 100,000 people per year, with up to 25% of cases starting during childhood or adolescence [1, 2]. Childhood-onset UC often begins as an extensive disease and can be additionally associated with linear growth impairment and delayed puberty, both caused by chronic inflammatory process [2]. Due to the special characteristics of this group, clinicians responsible must subject their patients to thorough clinical evaluation and tailor the treatment individually. This can be an unusually difficult task in the era of biologics, which on the one hand have revolutionized the treatment of inflammatory bowel diseases, while on the other, require careful monitoring and appropriate selection for a particular patient. Moreover, the course of UC in paediatric patients often involves multiple exacerbations and the subsequent need for several modifications of therapy [3].

We present a case report of an 11-year-old boy diagnosed with ulcerative colitis, who went through multiple lines of treatment during a 3-year period since diagnosis and is currently successfully treated with an off-label medication: vedolizumab.

CASE REPORT

The patient was referred to the hospital for the first time at the age of 7 years, with a history of intermittent loose bowel movements 5 months prior to admission. In the month before the admission, he had additionally experienced bloody stools and his condition had deteriorated.

ADDRESS FOR CORRESPONDENCE:
Ewa Antonina Biegańska, Student Research Association of Paediatric Emergency Medicine, Medical University of Warsaw, Warsaw, Poland, e-mail: ewabieganska2@gmail.com

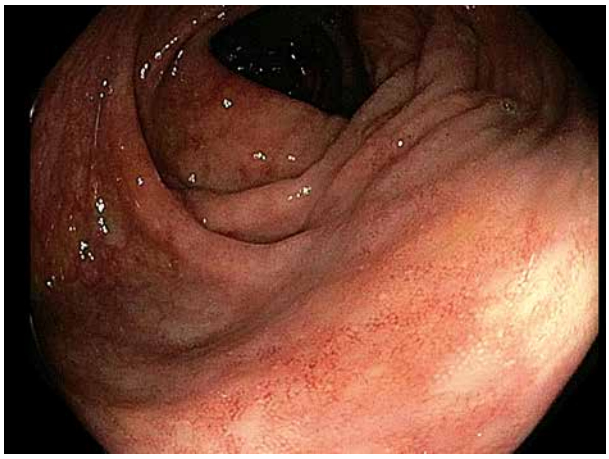

FIGURE 1. Image from the colonoscopy

Performed tests were positive for peripheral blood eosinophilia and revealed calprotectin levels above 10,000 μg/g. Stool cultures were negative for pathogens. Endoscopic examination of the oesophagus and colon revealed macroscopic features of eosinophilic esophagitis and UC with mild inflammatory changes, confirmed in histopathology (Figure 1).

The remission-inducing treatment included oral glucocorticosteroids (GCS), initially in full dose (prednisone 1 mg/kg bw) then gradually reduced, with simultaneous treat ment with full-dose azathioprine (2.5 mg/kg b.w. with controlled blood level of azathioprine metabolite (6-TG), which was within therapeutic limits) and mesalazine 70 mg/kg b.w. Clinical remission (bowel movements twice daily) was observed only during full-dose GCS treatment, but there was no mucosal remission – calprotectin levels were about 2000–3000 μg/g. However, it was decided to reduce the dose of steroids and to include local steroid treatment (budesonide), and mesalazine in suppositories for 3 months.

Despite the changed therapy, the patient presented symptoms of exacerbation: 6 bloody stools per day and elevated calprotectin concentration (8109 μg/g). Active inflammatory lesions were found with sigmoidoscopy, even though the blood level of azathioprine metabolite (6-TG) was correct. The decision was made to introduce experimental antibiotic therapy, which resulted in good clinical response, but not in mucosal recovery (calprotectin = 1143 μg/g). Next, the antibiotic treatment was modified by adding a 3-week course of rifaximin, but without any improvement. Subsequently, mesalazine was added in rectal infusions, but still without a positive response. On the contrary, aggravation of clinical complaints, and stools with blood appeared again. Oral and rectal mesalazine was discontinued, which resulted in lowering of calprotectin level and improvement of complaints (bowel movements one per day, no blood, no abdominal pain), raising the diagnosis of mesalazine intolerance.

Despite optimal treatment with azathioprine (6-thioguanine levels within the therapeutic range), after 5 months another exacerbation was observed; which was assessed as severe (PUCAI-70 pts). Because of inadvisable treatment with cyclosporine, the boy was qualified to biological treatment with infliximab (IFX). Endoscopic examination performed at that time revealed colitis ulcerosa-like lesions with involvement of the entire colon (pancolitis, Mayo 2 lesions), which was confirmed by magnetic resonance imaging (MRI). He received his first dose of IFX, which resulted in spectacular clinical improvement. Two weeks after the second induction dose, and then one week after the last induction of the 3rd dose, the boy presented a recurrence of symptoms. It was decided to escalate the biologic therapy (double dose of IFX every 4–6 weeks) with control of serum drug levels, because the blood tests revealed indeterminate levels of IFX and the presence of anti-IFX antibodies. Treatment with locally acting budesonide was added, along with continuation of azathioprine. Such a treatment regimen resulted in clinical, but not complete, mucosal remission. The clinical remission (PUCAI 10), but not mucosal (calprotectin concentration within 400 μg/g), was maintained at a similar level for a few months.

Because of the increase in inflammatory markers, which was observed during follow-up (ESR = 22 mm, calprotectin > 2000 μg/g), it was decided to maintain intensive biological and immunosuppressive treatment, with high IFX serum concentration (> 12.4 μg/ml).

The gradual loss of clinical remission (again, up to 5 loose stools with blood and PUCAI score 40–50), with a further increase of inflammatory markers (ESR = 34 mm/h, positive stool for occult blood, calprotectin level 256 μg/g), was observed, despite therapeutic IFX concentrations in the serum. This led to the loss of response to anti-TNF biologic therapy recognition, and a full diagnostic re-evaluation of the patient was planned.

During the hospitalization macroscopic features of exacerbation (Mayo 2) were detected by endoscopic examination. Additionally, a very high calprotectin concentration (2888 μg/g) was noted. Stool cultures were negative for pathogens, and cytomegalovirus infection in the colonic tissue was excluded. Abdominal MRI showed inflammatory lesions in the colon. Re-examination for anti-IFX antibodies appeared negative, and the serum IFX concentration was 17.6 μg/ml. Despite therapeutic doses of azathioprine, the clinical symptoms aggravated, and the patient's condition worsened. A progressive decrease in the rate of body weight gain (change of 2 percentile channels since the beginning of treatment) and deterioration of his general condition were observed. Thus, the decision was made to discontinue the IFX and to start methotrexate and nutritional treatment.

Despite intensive pharmacotherapy, the patient remained in severe exacerbation of the underlying disease. He had up to 8 completely unformed stools with blood, daily complaints of abdominal pain (5–8 on the VAS scale), elevated inflammatory markers in laboratory tests, and elevated stool calprotectin levels. Severity of the dis-

ease on the PUCAI scale was assessed at 65 points, which indicated a very serious form of UC.

Due to exhaustion of available therapeutic options, it was decided that anti-integrin treatment (vedolizumab) would be used in terms of the emergency access to rescue therapy, which is not routinely financed by the national insurance health company. The application was approved, and the patient started vedolizumab therapy exactly 3 years after the first diagnosis of ulcerative colitis and the beginning of therapy.

Over the course of treatment with vedolizumab, clinical symptoms gradually resolved and faecal calprotectin levels decreased. Currently, the patient is after the 9th dose of vedolizumab, in his 15th month of the reformulated therapy, and he remains in both clinical and mucosal remission, which had not been achieved with any other previous treatment option.

DISCUSSION

Paediatric-onset UC is generally thought to have more aggressive course than the adult-onset disease because it is frequently associated with a severe phenotype [4, 5]. Up to 40% of children present with pancolitis, and most have a high probability of disease extension and subsequently of surgical intervention with colectomy [6–8]. The disease burden remains high despite the introduction of biologics to the treatment regimens, which have revolutionized treatment of both paediatric- and adult-onset inflammatory bowel diseases [4, 7, 9]. Hence, there is a strong need for a continuous search for new treatment options, such as the new types of biologics, like vedolizumab.

Vedolizumab is a gut-selective integrin antagonist with no systemic immunosuppressive activity. It binds to integrin α4β7 expressed on T cells and prevents their migration to the gastrointestinal tract [10]. Because of its specificity it does not act on other organs and systems, which significantly limits the emergence of systemic adverse reactions [11, 12]. It has been proven as an effective treatment option in inducing and maintaining remission, both in UC and Crohn's disease in adults. It is currently recommended, and registered, as one of the available biologics that can be used in moderate and severe types of those diseases [13, 14].

In the paediatric population, however, data considering the efficacy and safety of vedolizumab are still limited. The majority of currently available studies are observational and based on retrospective cohorts, which are additionally limited to patients, who failed to respond to anti-TNF therapy. The reason for this may be that vedolizumab is currently identified in the recommendations as a drug possible to consider specifically in the absence or loss of response to anti-TNF therapy. What is more, it does not have registration for the paediatric age group, so therapy with vedolizumab is an off-label treatment [15, 16]. Nevertheless, it is noteworthy that in the available studies vedolizumab tends to present statistically significant remission rates, even higher than in the adult cohorts of anti-TNF refractory patients [12].

In a literature there are a few studies describing thed effectiveness of treatment of paediatric patients with either UC or Crohn's disease. These studies, while not describing large groups, report efficacy in inducing remission ranging from less than 40% to more than 80%. That is particularly impressive because these are mostly patients who either have not responded or have lost response to previous lines of therapy, including anti-TNF therapy. It may indicate that in some cases treatment with vedolizumab might give better results than anti-TNF therapy. At the same time it seems to be a safer treatment option, because its action is gut-specific, and there are a few adverse events reported in the literature.

In our belief, supported by literature data, vedolizumab should be considered as an available option in paediatric recommendations for treatment of inflammatory bowel diseases, as it already is for adults. It is likely that currently pending clinical trials, focused on testing the efficacy of vedolizumab in the induction of remission in paediatric patients with moderately to severely active UC, may contribute to this change. One of them, the HUBBLE trial, has recently been completed and the results published, and a phase III study is ongoing [17]. The presented case is an attempt to look at the effectiveness of the drug in the group of patients in whom long-term remission has not been achieved, and therefore the suggestion of including vedolizumab in funding programs should be considered.

CONCLUSIONS

In the case of our patient, vedolizumab was the only medication that induced a long-term clinical and mucosal remission. During the 3 years of his ailment the boy underwent all lines of therapy, which are registered to date. What is more, he also presented resistance to some of them, such as intolerance to mesalazine and the development of antibodies to IFX, despite concomitant therapy with azathioprine. It might be that in the future we will be able to identify a group of patients, who may respond better to therapies other than anti-TNF biologics.

DISCLOSURE

The authors declare no conflicts of interest.

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