

©Borgis

*Sylwia Fabiszewska, Grzegorz Oracz, Jarosław Kierkuś

Vedolizumab therapy in pediatric inflammatory bowel disease – case report

Leczenie wedolizumabem nieswoistych zapaleń jelit u dzieci – opis przypadku

Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Health Institute, Warsaw
Head of Department: Professor Marek Woynarowski, MD, PhD

Keywords

vedolizumab, inflammatory bowel disease, children

Słowa kluczowe

wedolizumab, nieswoiste zapalenie jelit, dzieci

Conflict of interest

Konflikt interesów

None

Brak konfliktu interesów

Address/adres:

*Sylwia Fabiszewska
Klinika Gastroenterologii, Hepatologii,
Zaburzeń Odżywiania i Pediatrii
Instytut „Pomnik – Centrum Zdrowia Dziecka”
Al. Dzieci Polskich 20, 04-730 Warszawa
tel. +48 (22) 815-73-84
s.fabiszewska@ipczd.pl

INTRODUCTION

Inflammatory bowel disease (IBD) is a broad term used to describe disorders of chronic inflammation of digestive tract. There are two types of IBD – ulcerative colitis and

S u m m a r y

Inflammatory bowel disease (IBD) is a term, which includes ulcerative colitis (UC) and Crohn's disease (CD) – chronic inflammatory bowel diseases with unknown etiology.

Disease is commonly thought to be caused by combination of immunological, genetic and environmental factors. Most often diagnosis of IBD is established among young, 15-29 years old people, but the age of diagnosis is systematically reduced.

Treatment plan depends on phase of disease, symptoms intensity and patient age.

The main type of treatment are enteral nutrition, pharmacological therapy and finally surgical intervention in case of insufficient response.

Until now, in pediatric patients U.S. Food and Drug Administration (FDA) approved biologic agents, infliximab and adalimumab as CD treatment and infliximab only as UC treatment.

Currently new biological agents are being studied as part of effective and safe IBD therapy in children. Particular attention is now given to vedolizumab which is already used and approved as part of IBD treatment algorithm in adults.

Purpose of this article is to present two cases in which vedolizumab was used in CU as well as CD therapy in pediatric patients.

S t r e s z c z e n i e

Nieswoiste zapalenie jelit (NZJ) to pojęcie, które obejmuje wrzodziejące zapalenie jelita grubego (WZJG) oraz chorobę Leśniowskiego-Crohna, czyli przewlekłe choroby zapalne jelit o nieustalonej etiologii.

Uważa się, że główną rolę w patogenezie pełnią czynniki immunologiczne, genetyczne oraz środowiskowe. Najczęściej choroba jest rozpoznawana u osób młodych pomiędzy 15. a 29. rokiem życia, ale wiek, w którym się ujawnia, systematycznie ulega obniżeniu.

Leczenie jest uzależnione od fazy choroby, nasilenia objawów i od wieku pacjenta. Stosuje się leczenie żywieniowe, farmakologiczne oraz w razie braku poprawy – leczenie chirurgiczne.

Dotychczas, amerykańska Agencja Żywności i Leków (Food and Drug Administration – FDA) dopuściła leki biologiczne do leczenia choroby Leśniowskiego-Crohna wśród dzieci – infliksymab oraz adalimumab, natomiast do leczenia wrzodziejącego zapalenia jelita grubego wśród dzieci – wyłącznie infliksymab.

Cały czas trwają poszukiwania nowych leków biologicznych, które byłyby skuteczne i bezpieczne w terapii NZJ u dzieci. Szczególną uwagę zwraca się obecnie na vedolizumab, który jest już oficjalnie dopuszczony przez Agencję Żywności i Leków do leczenia NZJ u dorosłych.

Celem tego artykułu jest prezentacja dwóch przypadków klinicznych dzieci, u których zastosowano vedolizumab w leczeniu NZJ.

Crohn's disease. The etiology of IBD isn't fully discovered, but proinflammatory cytokines are considered to be the main factor in pathogenesis, which is clearly used in therapeutical options for example biological treatment.

Currently we still observe development in this area – a new biological therapy of vedolizumab has been recently widely considered as approval treatment of IBD in children.

Vedolizumab is a humanized IgG1 monoclonal antibody to the gut specific adhesion molecule – α 4 β 7 integrin that modulates gut lymphocyte trafficking. Its local effect, which is clearly big advantage of this drug has been confirmed in past research results (1).

Until now efficacy, safety and tolerability of vedolizumab in adults were established in large number of research studies. The most popular were GEMINI 1, 2 and 3. Vedolizumab was used in 300 mg intravenous doses in weeks: 0, 2, 6 and then every 4 or 8 weeks.

GEMINI 2 study focused on adult patients with moderately to severely active CD in whom 1 or more prior CD therapies had failed. Vedolizumab showed significant improvement in the primary endpoint of clinical remission (CDAI score \leq 150 points) at six weeks compared to placebo (14.5 vs. 6.8%) (2).

At week 52, 39.0% of the patients receiving vedolizumab every 8 weeks and 36.4% of those receiving vedolizumab every 4 weeks were in clinical remission, as compared with 21.6% of patients receiving placebo (2).

In the secondary endpoint at week 52, the proportions of patients who had a CDAI-100 response and who had glucocorticoid-free remission were significantly greater in the groups receiving vedolizumab every 8 weeks and every 4 weeks than in the placebo group (2).

Adverse events affected at least 5% of patients who received vedolizumab (at least one dose of study drug).

The most common adverse events reported in the vedolizumab arm were CD exacerbation, arthralgia, pyrexia, nasopharyngitis, headache, nausea and abdominal pain. The most common adverse events reported in the placebo arm were CD exacerbation, headache, arthralgia, pyrexia, abdominal pain, nausea and nasopharyngitis (2).

GEMINI 3 study is focused on moderately to severely active CD patients who had previously failed therapy with TNF α antagonists. Vedolizumab was not significantly more effective than placebo (15.2 vs. 12.1%) in inducing clinical remission at week 6 among patients with CD in whom previous treatment with TNF antagonists had failed. The therapeutic benefits of vedolizumab in these patients were detectable at week 10 – 26.6% of those given vedolizumab and 12.1% of those given placebo achieved clinical remission. Additionally 39.2% of patients with previous TNF antagonist failure given vedolizumab and 22.3% of those given placebo had a CDAI-100 response at week 6. Adverse event results were similar among all groups. Vedolizumab (similar to TNF antagonists) may have also a more pronounced effect in TNF antagonist-naïve patients than in patients with prior TNF antagonist failure (3).

GEMINI 1 was about vedolizumab as induction and maintenance therapy for ulcerative colitis. Vedolizumab demonstrated greater efficacy as CU therapy in adults compared to CD therapy and was significantly more effective than placebo in inducing clinical remission at week 6 among TNF-naïve patients (53.1 vs. 26.3%), as well as in TNF-failure population (39.0 vs. 20.6%). Vedolizumab is relatively more effective in TNF-naïve patients than TNF-failure patients (53.1 vs. 39.0%) (4).

As the most common adverse effects of vedolizumab were reported: nasopharyngitis, headache, arthralgia, and nausea. Longer-term safety trials are needed but based on evidence to date, there is no evidence of a higher odds of serious infections from the newly available biologic therapies, such as vedolizumab, compared to the anti-TNF agents (5) and also the progressive multifocal leukoencephalopathy (PML) associated with vedolizumab has not been reported (6).

CASE REPORT

Case 1

Child A was diagnosed at the age of 26 months with pancolitis (Mayo = 3) and suggestion of CU in endoscopy (September, 2013). At the beginning mesalazine and steroid treatment was applied with no clinical response. After two months second endoscopy confirmed persistent disease activity and diagnosis of CD was established (November, 2013). Infliximab with concomitant azathioprine and mesalazine was initiated with positive therapeutic effect (normalisation of stool pattern), but because of anaphylactic reaction during the second infusion of infliximab, therapy was switched to adalimumab (40 mg s.c. per dose). After a second dose of adalimumab the recurring fevers and infections requiring a number of different empiric antibiotic treatments occurred. Despite lack of rectal bleeding, anemization requiring blood transfusions appeared. Patient presented also non-specific skin eruption, increased inflammatory markers (CRP, OB, thrombocytosis) and electrolyte imbalance and increased number of stools (PCDAI 55). Decision about stopping adalimumab therapy was made. After trials of treatment: cyclosporine, again – adalimumab (40 mg s.c. per dose, 3 doses every 2 weeks was applied) and the lack of response to it combined with no improvement in a clinical condition of a patient (fevers, periodic anemization requiring blood transfusions, recurrent non-specific skin eruptions, increased number of abnormal stools with blood and mucus, failure to gain weight), a decision of ileostomy was made (April, 2014). After that patient was prescribed azathioprine and mesalazine. After 4 months from surgery clinical condition (PCDAI 2.5) as well as colonoscopic examination (in Paris Classification: A1a, L2, B1) showed improvement. Unfortunately clinical condition had been gradually declining (PCDAI 15-30) and after 16 months from surgery hospitalization for IBD exacerbations had

started again. In August of 2015 the methotrexat (7.5 mg s.c. once a week) was initiated together with the trial of Modulen diet which resulted in the improvement in clinical condition (PCDAI 10) and in a colonoscopic examination (October 2015 – loss of colonic haustration, but without acute inflammation in the large intestine). In April of 2017 in spite of relatively good clinical condition (PCDAI 10) in a process of performing endoscopic evaluation a severe inflammation in distal part of sigmoid colon was established, which forced the endoscopist to discontinuation of the examination. A subtotal colectomy would have been the next therapeutic step, but the parents didn't authorized it. Instead parents consented to off-label treatment with vedolizumab in their child, because of the recent promising result of vedolizumab therapy in adults. 150 mg vedolizumab (intravenous, 10 mg/kg/dose) was applied. The second dose was separated from the previous one by 18 days, the third dose – by another 4 weeks. Currently treatment consists of vedolizumab with concomitant mesalazine (500 mg) and metotrexat (7.5 mg s.c. per week). Currently patient is in good clinical condition (PCDAI 5), further vedolizumab treatment with control endoscopic examination is planned.

Case 2

Child B was diagnosed at the age of 2 with severe pancolitis in endoscopy (at the beginning of 2012). Because it wasn't possible to differentiate ulcerative colitis and Crohn's disease, the exact diagnosis couldn't be established. Quick clinical remission was achieved after full course of steroids, azathioprine and mesalazine. After one year clinical condition of this patient worsened (relapse of rectal bleeding, increased number of stools) and endoscopy showed enhanced inflammation, Mayo 3 (April, 2013). Diagnosis of ulcerative colitis was established. After next year of frequent disease relapses (increased number of stools, rectal bleeding, severe colitis in endoscopic examinations), decision to initiate infliximab was taken (July, 2014). Almost three months after first dose of anti-TNF (in total 4 doses of infliximab) there was only a partial response. Sigmoidoscopy showed severe colitis (December, 2014). The trial of cyclosporine therapy didn't have any positive effect. During following two years frequent relapses were observed, which were treated with full courses of steroids and increased doses of azathioprine (62.5 mg per dose – 3.9 mg/kg). In January of 2017 endoscopic examination showed moderate inflammation up to hepatic flexure of the colon (Mayo 2, E 4), PUCAI in that time was 10. A trial to unable cyclosporine was renewed (February, 2017, around 8 mg/kg/day in two doses) and clinical remission was achieved. However due to high blood pressure and an increased level of hirsutism, the treatment was stopped and adalimumab was initiated (April, 2017, 40 mg s.c. per dose). There

was a quick response to this treatment which lasted four months (PUCAI 0). In fifth dose of adalimumab, a disease flare occurred (August 2017). Because of severe trajectory of relapse (PUCAI 60-70) combined with electrolyte imbalances (hyponatremia, hypokalemia, hypochloremia), increased inflammatory markers and nutrition problems, intravenous steroid therapy, antibiotics and total parenteral nutrition was applied followed by the initiation of vedolizumab as off-label treatment (September, 150 mg *i.v.*). The second dose was separated from the first one by 2 weeks. After two doses of vedolizumab combined with reduction of steroids therapy normalization of the stools and improvement in laboratory tests were observed gradually (PUCAI 20). Third dose of vedolizumab was delayed because of pulpitis requiring tooth extraction. Patient is in the relatively good clinical condition (PUCAI 10-15), further vedolizumab treatment with control colonoscopic examination is planned.

DISCUSSION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing and remitting diseases of the bowel. Current knowledge of pathogenesis of IBD has improved and is still developing. However the number of IBD incidents among the pediatric population is still rising. Because of the increase of available drugs and treatment options, the risk of surgery has decreased significantly. The progress in the therapeutic options and a number of new drugs allow us to provide the individualized and optimized therapy and to achieve very important goals in young patients – growth, overall well-being, emotional health and improved quality of life. Increasingly we are able to achieve deep remission, which means not only symptomatic but also mucosal remission.

Currently, vedolizumab is widely discussed as one of treatment strategies. The number of studies which presents encouraging data of safeness and effectiveness in pediatric refractory IBD is recently increasing (7, 8). Previous findings suggest that vedolizumab is characterized with earlier and higher rates of remission in UC patients compared to CD patients and in anti-TNF-naive patients compared to those with anti-TNF exposure (7, 8).

Majority of available studies of vedolizumab in children is limited by quite small sample size, frequent previous treatment with anti-TNF medication and retrospective nature of study.

CONCLUSIONS

In children, it seems that vedolizumab should be for now reserved for patients who have exhausted other treatment options.

A larger study with longer follow-up period is definitely required but previous data are encouraging.

BIBLIOGRAPHY

1. Wyant T, Leach T, Sankoh S et al.: Vedolizumab affects antibody responses to immunisation selectively in the gastrointestinal tract: randomised controlled trial results. *Gut* 2015; 64(1): 77-83.
2. Sandborn WJ, Feagan BG, Rutgeerts P et al.: Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013; 369(8): 711-721.
3. Sands BE, Feagan BG, Rutgeerts P et al.: Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology* 2014; 147(3): 618-627.
4. Feagan BG, Rubin DT, Danese 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(2): 229-239.
5. Wheat CL, Ko CW, Clark-Snustad K et al.: Inflammatory Bowel Disease (IBD) pharmacotherapy and the risk of serious infection: a systematic review and network meta-analysis. *BMC Gastroenterol* 2017; 17(1): 52.
6. Cherry LN, Yunker NS, Lambert ER et al.: Vedolizumab: an $\alpha 4\beta 7$ integrin antagonist for ulcerative colitis and Crohn's disease. *Ther Adv Chronic Dis* 2015; 6(5): 224-233.
7. Ledder O, Assa A, Levine A et al.: Vedolizumab in Paediatric Inflammatory Bowel Disease: A Retrospective Multi-Centre Experience From the Pediatric IBD Porto Group of ESPGHAN. *Crohns Colitis* 2017; 11(10): 1230-1237.
8. Singh N, Rabizadeh S, Jossen J et al.: Multi-Center Experience of Vedolizumab Effectiveness in Pediatric Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2016; 22(9): 2121-2126.

received/otrzymano: 05.10.2017
accepted/zaakceptowano: 25.10.2017