Successful Treatment with Infliximab in a Case of Crohn's Disease with Peripheral Arthropathyes

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Introduction: Crohn disease is an inflammatory bowel disease that involves any region of the alimentary tract from the mouth to the anus and it is transmural. Children with early onset are more likely to have colonic involvement. Infliximab constitutes today one of major therapeutic approaches at cases of Crohn's disease.

Material and methods: We present the case of a 15-year-old female who was admitted in our department presenting pain of the large joints (exacerbated by movement), abdominal pain (epigastric and hypogastric), vomiting, diarrhea. In order to induce remission of the disease, we chose the step-up therapy (the only one accepted in Romania for children with Crohn disease). The initial response to immunosupressant therapy was moderate: no digestive symptoms were present, but extradigestive (articular) symptoms were still present and remission was not obtained (inflammation markers were still present and PCDAI was still above 15). We decided to try to induce remission with Infliximab.

Results: We obtained only temporary improvement of symptoms with "classical" therapy. We had a good response to Infliximab (remission was obtained), but treatment discontinuation without medical advise led to relapse after 9 months.

Conclusions: Infliximab was effective as therapy in Crohn's disease with peripheral arthropathy, but too soon discontinuation of treatment due to patient's non compliance determined relapse of the disease.

Keywords: Crohn's disease, peripheral arthropathy, Infliximab, relapse

Introduction

Inflammatory bowel disease includes two distinctive disorders (Crohn's disease and ulcerative colitis) of idiopathic chronic intestinal inflammation, characterized by unpredictable exacerbations and remissions. Crohn's disease involves any region of the alimentary tract from the mouth to the anus and it has transmural character. Its evolution can associate local or systemic, sometimes severe complications [1]. A variety of joint involvement has been described, from large joint pauciarticular arthropathy to a rheumatoid pattern polyarthropathy. Enteropathic peripheral arthropathy without axial involvement can be subdivided into a pauciarticular, large joint arthropathy, and a bilateral symmetrical polyarthropathy [2].

In cases of Crohn's disease associating extraintestinal manifestations, the recommendation is to use biological treatment [3]. The only biologic drug approved in children with Crohn's disease in Romania is Infliximab. It is a chimerical monoclonal antibody (75% human and 25% mouse) directed against tumoral necrosis factor alpha (TNF-α), cytokine with important role in inflammatory activity of disease [4]. The use of Infliximab is associated with significant reduction of intestinal inflammation and clinical favorable response [1].

Material and method

We present the case of a 15-year-old female, from urban habit, with a particular onset of Crohn's disease. We have the written consent, signed by her mother, to publish this article.

She came to First Pediatric Clinic Timisoara, being admitted at the end of March 2008, for pain of the large joints (exacerbated by movement), abdominal pain (epigastric and hypogastric), vomiting, diarrhea (5 stools/day), which were present for six weeks.

Physical examination revealed a good general condition, relative normal stature and weight. Data were pertained to 2007 WHO growth standards. (67 kg, 1.67m heigh, BMI = 24 kg/m^2 – percentile 85%). The abdomen was tender at palpation, cardiological examination revealed low degree mitral insufficiency.

Blood sample analysis revealed increased leucocytes number (24 500 WBC/mm^3), with neutrophilia (72.3%), high inflammation (erythrocytes sedimentation rates [ESR] 100mm/h, positive C-reactive protein [CRP] 22.4 mg/l and fibrinogen [fbg] 7.65 g/l); hypochromic anemia with iron deficiency. (Hemoglobin [HGB] 10g/dl, hematocrit [HCT] 31.1%, mean corpuscular volume [MCV] 69fL, mean corpuscular hemoglobin [MCH] 20.9 pg, mean corpuscular hemoglobin concentration [MCHC] 28.5 g/dL, blood iron concentration [Fe] 5.1 μmol/L). All the other analysis were normal. Immunologichal markers such as anti-neutrophil cytoplasmic antibodies (ANCA), anti-saccharomyces cerevisiae antibody (ASCA), antibodies to tissue transglutaminase (anti-tTG) and anti-streptolysin O antibody (ASLO), lupic cell, human leucocyte antigen B 27 [HLA B27] were all negative. Bacteriological tests (cultures from nose, pharynx, bloodstream, urine, stool) wear also sterile.

Abdominal ultrasound sowed thickening of intestinal wall. Magnetic resonance imaging (MRI) revealed inflamated lymph nodes (intraperitoneal, perimesentheric, juxtaintestinal) with maximum size 2 cm.

Endoscopical examination was performed up to the hepatic flexure. It showed a small ulceration and erythemathous area at the rectosigmoid junction. A large ulcer (~ 3 cm) covered by fibrin, with red inflamed edges was observed in the sigma. The descending colon presented several ulcers with pseudopolypoid edges. The splenic flexure had a normal layout. Transverse colon had several ulcers with pseudopolypoid edges and polyps. The presence of faeces imposed the cessation of the examination. Microscopic examination of the mucosal fragments obtained from ulcers, ulcer edges, and polyps demonstrated changes that are highly suggestive for Crohn's disease (mucosa with extensive ulceration, the base of ulceration consisting of granulation tissue, with rich vessels network, lympho-plasmocytic infiltrate); chronic inflammatory infiltrate with gigantic cells and lymphocytic aggregates.

Ophthalmologic examination revealed no pathologic findings. Gynecologic examination established the diagnoses of pelvic inflammatory disease.

We established the diagnoses of Crohn disease, pelvic inflammatory disease, hypochromic anemia. The Pediatric Crohn Disease Activity Index (PCDAI) calculated in March 2008 counted 37.5 points (normal value < 15). We intended to induce remission. We chose the step-up therapy (the only one accepted in Romania for children with Crohn's disease). We prescribed specific treatment with Budesonid (9 mg/day), Mesalasine [Salofalk] (2 g/day). We also prescribed antibiotic – Ciprofloxacin (1g/day) for 12 days, after that Metronidazole. To treat other simptoms we prescribed Drotaverinum [No-spa] , Trimebutin maleat [Debridat], Pantoprazolum [Controloc]. Enterol alernatively with Biotics was given for intestinal flora. To treat anemia we administrated Folic acid, Pikovit and later Ferrogradumet.

With this therapy the clinical evolution was good: no digestive symptoms were present, articular symptoms were also absent, the inflammation markers decreased (but did not normalize). In May 2008 after 3 months of treatment with Budenofalk and Mesalasine, ESR was 45 mm/h, CRP 20.78 mg/l. Symptoms being absent, we continued the treatment, but we found a raise of inflammation markers (in June and July ESR increased to 60 and then to 65, CRP also increased first to 31.95 mg/l then to 51.02 mg/l). In July we performed another endoscopy. We observed a light improvement of the sigma and the rectal-sigmoid junction aspect. But the splenic flexure was still involved and transverse colon had almost the same aspect. This time we succeed to perform endoscopy till terminal ileum. We found the same modification of the mucosa including ulcers, pseudopolyps. Microscopic aspects were very similar to the previous. During this period a loss of weight was also registered (8 kg, representing 11.9 %)

In this situation we decided to try to induce remission with Infliximab 5 mg/kg/dose, given in three infusions for induction, over a six weeks period (at 0, 2, and 6 weeks) and after that, every 8 weeks for maintenance.

We calculated PCDAI at the beginning of biologic therapy and we found out that it was still 35 points. Four weeks later we obtained remission, PCDAI was significantly reduced (5 points). After 8 weeks it was still decreased (2.5 points). We continued with maintenance therapy (other 4 doses). No side effects were observed and PCDAI remained steady at 0 points, but against medical recommendations she discontinued therapy after the 7th dose. Nine months after discontinuation she came back with relapse (abdominal and articular pain, diarrhea, increased inflammatory markers (CRP 37.5 mg/l, ESR 55 mm/h), PCDAI counted 25 points. We determined fecal calprotectin to asses bowel inflammation and we obtained a value of 1970 μg/g (normal range is less than 50 μg/g). We recommended colonoscopy to asses colic lesions before deciding the therapeutically approach, but she refused. She continued therapy with corticosteroids [Budenofalk] 9 mg/day. Three months later symptoms still persist (abdominal pain, diarrhea: 2–3 stools per day, articular pain – arthritis of the right knee). Inflammatory markers were even higher than before (CRP 76.24 mg/l, ESR 70 mm/h). We reexplained her the necessity of Infliximab and the importance of maintenance therapy. She accepted the continuation of Infliximab. We administrated 300 mg/dose [5 mg/kg] of Infliximab every eight week. After the third dose remission was obtained (no abdominal pain, normalized stools, no articular pain).

Results

We obtained only temporary improvement of symptoms with "classical" therapy. We had a good response to Infliximab (remission was obtained) and no side effects, but treatment discontinuation after the 7th dose (3 for induction and other 4 for maintenance) without medical advise led to relapse after 9 months. After discontinuation of Infliximab, three months treatment with corticosteroids wasn't effective neither on digestive symptoms nor articular. Reintroduction of Infliximab reinduced remission.

Discussions

Among children with Crohn's disease, the initial presentation most commonly involves ileum and colon (ileocolitis) [4], the disease has a predilection for the distal small bowel and proximal colon.

Abdominal pain may be the initial symptom of Crohn's disease. It is often accompanied by diarrhea, especially in those who have had surgery. The diarrhea may or may not be bloody. Visible bleeding in the feces is less common in Crohn's disease than in ulcerative colitis, but may be seen in the setting of Crohn's colitis [5].

Crohn's disease is associated with seronegative spondyloarthropathy. This group of diseases is characterized by arthritis or enthesitis. The arthritis can affect larger joints, such as the knee or shoulder, or may exclusively involve the small joints of the hands and feet. The symptoms of arthritis include painful, warm, swollen, stiff joints and loss of

joint mobility or function [6]. Our patient first presented with arthropathy.

Typically, therapy for pediatric Crohn's disease is administered in a step-up approach[7]. More recently, adult data have supported the use of biological therapy earlier in the course of disease (a "step-down" approach) as a more effective treatment method [8].

It is essential to consider the adverse consequences of therapy, particularly with regard to any durable consequences of short-term treatment and adverse effects of maintenance therapy [9].

In a prospective, open-label trial, Kugathasan S et al. intended to determine whether Infliximab treatment would be benefit for pediatric patients with medically refractory Crohn's disease. 94% improved after Infliximab infusion, with a significant decrease of both PCDAI and daily steroid use by 4 wk, 67% achieved complete remission by 10 wk. The authors also assessed the duration of response: 50% children with early disease maintained clinical response through the 12-month trial period none with late disease. We may consider our patient with early disease, and although we administrated maintenance therapy four doses, relapse occurred 9 months after discontinuation.

Scheduled, maintenance therapy with Infliximab has substantial clinical benefits (compared with episodic treatment) in patients who achieved remission with initial Infliximab induction therapy [10-13]. The study of maintenance therapy (ACCENT I) sowed that initial clinical response was maintained significantly more often in the groups that received scheduled maintenance therapy (43 and 53 versus 17 percent in the 5 mg/kg, 10 mg/kg versus single dose groups, respectively). After 54 weeks, the median duration of response was only 19 weeks for patients in the single dose group, compared to 38 weeks for the Infliximab 5 mg/kg every eight weeks group, and greater than 54 weeks for patients in the infliximab 10 mg/kg every eight weeks group.

There are several acute reactions described in literature: anaphylactic and anaphylactoid reactions, serum sickness-like reactions or antibody to Infliximab (ATI).

Premedication is often routinely given before infusions, consisting of paracetamol, antihistamines and/or corticosteroids, to prevent the occurrence of infusion reactions [14]. For betamethasone there was no significant difference compared to placebo. And for intravenous hydrocortisone there was a lower percentage of infusion reactions (24% vs. 15% for placebo), but these results were also not significant [15]. However, solid evidence that prophylactic medication can prevent infusion reactions is lacking [14].

We administrated Paracetamol iv [Perfalgan] and Levocetirizinum po [Xyzal] before all infusions. No allergic reaction occurred in the case presented.

Toxicity – the ACCENT I (performed on adults) study showed that infusion reactions were more frequent in the regularly scheduled groups (a reaction occurred in 6 percent of each regularly scheduled 5 mg/kg infusion compared with 3 percent of each episodic infusion). Otherwise, toxicity was generally similar between the groups. Serious infections occurred in 3 to 4 percent of all groups. There were six malignancies (1 percent overall), all randomly distributed between the groups. There were three deaths (one due to sepsis) [10].

The SONIC study (performed on adults) demonstrated that patients with moderate to severe CD treated with the azathioprine (2.5 mg per kg daily) in combination with Infliximab (5 mg per kg at weeks 0, 2 and 6 and then every eight weeks), or Infliximab alone, are more likely to have a glucocorticoid-free clinical remission than azathioprine alone (57 and 44 versus 30 percent, respectively) [16]. The occurrence of hepatosplenic T-cell lymphomas in patients on Infliximab (or other anti-TNF biologics) in combination with Azathioprine or 6 mercaptopurine (6-MP), opportunistic infections in patients on more than one immunosuppressive agent, led to the recommendation that infliximab be given as monotherapy without concomitant immunosuppressives.

We registred no toxicity or other side effect, but the time we observed for malignancies was really short.

Conclusion

Arthropathy was the initial manifestation of Crohn's disease in the case we present. We obtained only temporary improvement of symptoms with "classical" therapy. Infliximab was effective therapy in Crohn's disease with peripheral arthropathy, but too soon discontinuation determined relapse. It was effective on both digestive and articular symptoms. The disappearance of symptoms and improvement of Quality-of-life contributed to the patient's non-compliance. She stopped the treatment with Infliximab, against medical advise, although we explained her the importance of maintenance therapy due to the chronic evolution of Crohn's disease. This proves the importance of communication between doctor and patient.

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