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Infliximab treatment of pediatric refractory Crohn's disease: A case report

Tedaviye dirençli pediatrik Crohn hastalığında Infliksimab tedavisi: Olgu sunumu

Sezin AŞIK AKMAN[1], Çiğdem ARIKAN[2], Gülben SÖZEN[1], Can ÖZTÜRK[1], Raşit Vural YAĞCI[2]

Department of [1]Pediatric Gastroenterology, Hepatology and Nutrition Unit, Tepecik Teaching Hospital, İzmir

Department of [2]Pediatric Gastroenterology, Hepatology and Nutrition Unit, Ege University Medical School, İzmir

Infliximab is a monoclonal antibody that targets TNF-α and has been shown to be effective for the management of steroid-dependent or refractory Crohn's disease. It is an effective therapy in adult patients, but experience in children is limited. We report a case of Crohn's disease which was refractory to the conventional treatment. A 14-year-old boy was admitted to the hospital with arthralgia and oral and perianal lesions. On physical examination his body weight was below the 3rd percentile, and height was between the 3rd-10th percentiles. He had elevated erythrocyte sedimentation rate and C-reactive protein and decreased hemoglobin, hematocrit and albumin levels. Barium enema and computerized abdominal tomography revealed a markedly distended small bowel with a narrowed area just above the ileocecal valve and terminal ileum. There was no mucosal pathology in his colonoscopic study. A regimen of prednisolone was begun with a diagnosis of Crohn's disease. In the first month of therapy the patient experienced progressive worsening of his symptoms, and azathioprine was added to the treatment in the second month. As he had exacerbation of his symptoms and worsening laboratory tests, infliximab infusions (5 mg/kg/d) were administered intravenously (at 0, 2 and 6 weeks) at the end of the 8th week. At the 6th week of treatment including two infusions of infliximab at 0 and 2 weeks, clinical and laboratory response occurred. The only side effect of the treatment was pneumonia, which was seen after the 6th week of the therapy. In conclusion, infliximab appears to be an effective and safe therapy for childhood refractory Crohn's disease.

Key words: Crohn's disease, childhood, infliximab

İnfliksimab, steroide bağımlı veya tedaviye dirençli Crohn hastalığının tedavisinde etkili, TNF-α inhibitörü olarak rol oynayan bir monoklonal antikordur. Erişkinlerde tedavideki etkinliği kabul edilmesine karşın, çocukluk çağında kullanımı sınırlıdır. Konvansiyonel tedaviye yanıtsız Crohn hastalığı tanılı bir olgu sunulmaktadır. Artralji, ağız ve perianal bölgede lezyonlar nedeni ile hastanemize başvuran ondört yaşında erkek olgunun fizik bakısında ağırlığı %3'ün altında, boyu %3-10 bulundu. Eritrosit sedimentasyon hızı ve C-reaktif protein düzeyi yüksek; hemoglobin, hematokrit ve albümin düzeyleri ise düşük saptandı. Baryumlu kolon grafisi ve bilgisayarlı karın tomografisinde ileoçekal valv ve terminal ileumun üzerinde kalan bölgede darlık ve bu bölgenin proksimalinde incebarsak segmentlerinde genişleme belirlendi. Kolonoskopik değerlendirmede mukozal patoloji saptanmadı. Crohn hastalığı tanısı alan olguya prednizolon tedavisi başlandı. Tedavinin birinci ayında klinik bulguların giderek ilerlemesi üzerine, ikinci ayda tedaviye azatiopürin eklendi. İzlemde, hastalığın klinik ve laboratuvar bulgularının alevlenme göstermesi üzerine, tedavinin 8. haftasının sonunda infliksimab infüzyonu (5mg/kg/g) başlandı (0,2 ve 6. haftalarda). İnfliksimabın 0 ve 2. haftalarda uygulanan iki infüzyonunun ardından, tedavinin 6. haftasında klinik ve laboratuvar yanıta ulaşıldı. Altıncı haftada saptanan pnömoni dışında, tedaviye bağlı yan etki gözlenmedi. Sonuç olarak, infliksimab tedavisinin çocuklukta tedaviye dirençli Crohn hastalığında etkili ve güvenli bir tedavi olduğu düşünülmektedir.

Anahtar kelimeler: Crohn hastalığı, çocukluk çağı, infliksimab

INTRODUCTION

Crohn's disease (CD) is a chronic transmural inflammation that may involve any part of the alimentary tract from mouth to anus, but mainly distal ileum and colon. The first-line therapy of CD is a combination of aminosalicylates, antibiotics, steroids and immunomodulatory agents. Oral prednisone is the most frequent choice followed by azathioprine (AZA) (1, 2).

Medically- or surgically-induced remissions in CD are typically short-lived with almost inevitable recurrence of symptoms. Since CD is associated with high rates of relapse, current treatment regimens attempt to induce and maintain remission while minimizing toxic side effects. Chronic inflammation in CD can be attributed in part to the increased production of inflammatory cytokines, especially

Address for correspondence: Sezin AŞIK AKMAN
1401 Sok. No: 24/2, 35220 Alsancak, İzmir, Turkey
E-mail: dr.akman@superonline.com.tr

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tumor necrosis factor-alpha (TNF-α). Several studies have shown that TNF production in the intestinal mucosa is increased in patients with CD. Infliximab is a monoclonal antibody that targets TNF-α and has been shown to be effective for the management of steroid-dependent or refractory CD. It is an effective therapy in adult patients, but experience in children is limited (3-6).

We report a case of a 14-year-old-boy with CD who was refractory to conventional treatment and was treated with infliximab therapy.

CASE REPORT

A 14-year-old boy was admitted to our hospital with arthralgia affecting the knees. He had also been suffering from oral and perianal wounds for the last six years. He had a two-year history of intermittent episodes of abdominal pain and arthritis in lower extremities. His father was seropositive for hepatitis B virus antigen, and his mother had stomatitis several times a year. On physical examination his body temperature, pulse and blood pressure were normal. His body weight was below the 3rd percentile (-2.4 SDS), and height was between the 3rd and 10th percentiles. There were several painful, aphthous lesions on his lips and ulcerous lesions on buccal and perianal mucosa. Laboratory investigations revealed low leukocytes, hemoglobin, hematocrit, and albumin; high thrombocytes, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) levels; and normal liver and kidney function tests (Table 1). His ophthalmologic examination was normal. Pathergy test, antinuclear antibody, antineutrophil cytoplasmic antibody (p-ANCA, c-ANCA) and tuberculin skin tests were negative. Chest X-ray was normal. The patient underwent an extensive evaluation of the gastrointestinal tract. Upper gastrointestinal endoscopy showed chronic antral gastritis. Barium enema and computerized abdominal tomography revealed a markedly distended small bowel with a narrowed area just above the ileocecal valve and terminal ileum (Figure 1). No mucosal pathology was found by upper and lower endoscopic and colonoscopic studies. The patient was diagnosed as CD based on the history of intermittent episodes of abdominal pain and arthralgia accompanied by recurrent painful, aphthous buccal and perianal mucosal lesions and growth retardation, laboratory findings of elevated acute phase reactants, and radiological evaluation. A regimen of prednisolone was begun (2 mg/kg/d, max 60 mg, PO). In the first month of therapy the patient experienced progressive worsening of symptoms, so an immunosuppressive agent, azathioprine (AZA, 2 mg/kg/d, PO) was added to the treatment in the second month. During his follow-up, symptoms recurred with abdominal pain episodes and aphthous lesions in his mouth. Laboratory tests, performed every four weeks, revealed high levels of ESR and CRP accompanied by thrombocytosis. At the end of the 8th week, the patient was accepted as refractory to the first-line therapy modalities and

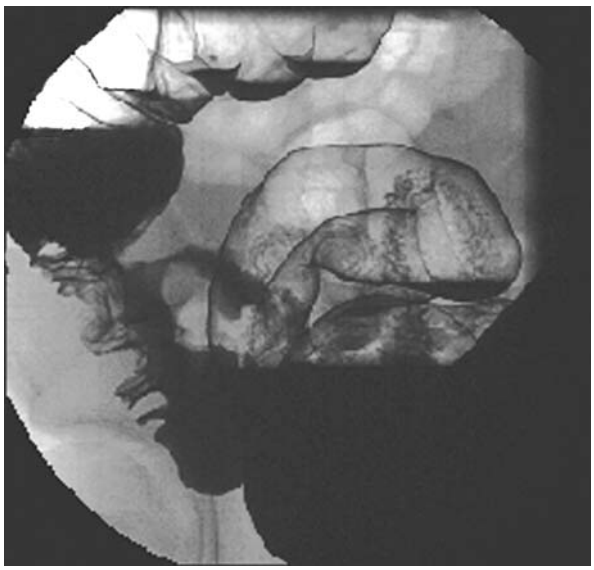

Figure 1. Barium contrast enema radiography

Table 1. Laboratory findings of patient at baseline and pre- and post-infliximab periods

	Baseline	Pre-infliximab	2nd dose infliximab	3rd dose infliximab	Post-infliximab
Hb (g/dl)	10.2	10.1	11.5	12	12.6
Ht (%)	32	31.2	36.7	39	40.9
PLT (mm^3)	576000	408000	287000	274000	256000
Sed (mm/hr)	57	49	20	11	8
CRP (mg/dl)	7.05	4.87	0.63	0.35	0.15
T. prt (g/dl)	6.9	7.2	7	7.3	7.8
Alb (g/dl)	3.1	4.1	4.4	4.6	4.7

Hb: Hemoglobin, Ht: Hematocrit, PLT: Platelets, Sed: Erythrocyte sedimention rate, CRP: C-reactive protein, T. prt: Total protein, Alb: Albumin

infliximab infusions (5 mg/kg/d) were administered intravenously (at 0, 2 and 6 weeks). His symptoms resolved dramatically soon after beginning the infusions (Table 1). After the third dose of infliximab, his symptoms and laboratory abnormalities disappeared. Azathioprine and steroid therapy was continued at the dose of 1 mg/kg and 15 mg/d, respectively, for the next months (alternate therapy). Infliximab treatment was continued every eight weeks until week 54 (total nine doses). At the 6th week of the infliximab treatment, the dose of AZA was dropped to 1 mg/kg from 2 mg/kg and the dose of the steroid (60 mg/d) was also decreased 5 mg every week until the alternate dose of 15 mg/d was reached. The only side effect of the treatment was pneumonia, which was seen after the 6th week of the therapy and it was responsive to antibiotic treatment. There was no other adverse event during therapy. Laboratory and radiological evaluation at the 30th week of the therapy revealed a normal ESR, CRP and serum albumin levels.

Our patient is now on the 20th month of his treatment, and infliximab infusions have been stopped. He is still receiving alternate steroid (15 mg/d) and AZA (0.75 mg/kg) therapy. Symptoms did not recur after discontinuation of the infusions.

DISCUSSION

Therapeutic options for CD are diverse. Traditionally, mild to moderate disease has been managed sequentially, initially with less toxic medications such as 5-aminosalicylic acid preparations (5-ASA), followed by steroids and immune suppressive agents. Steroids plus AZA has been found to be beneficial in reducing disease activity and inducing remission (2, 7). However, standard therapy of CD is associated with limited efficacy.

Recent advances in CD immunopathology have led to the use of new immune suppressants that block inflammation in the earlier step (2). CD is characterized by up-regulated intestinal inflammation mainly caused by increased TNF-α levels (8). Infliximab, a monoclonal antibody against TNF, is an effective maintenance therapy for patients with CD. Infliximab produces significant endoscopic healing and improvement of both laboratory signs and quality of life scores (5, 9, 10). A placebo-controlled trial described healing of active disease in 65% of CD patients compared to a rate of 17% with placebo. The response seen was rapid and often occurred within one to two weeks of the initial dosage (11). In another pediatric study (2), infliximab was judged to be effective in 96.4% of patients who had steroid refractory disease. Targan et al. showed that a single infusion of 5 mg/kg of chimeric monoclonal antibody against TNF (infliximab) induced a clinical response in 81% and clinical remission in 48% of CD patients, compared with 17% and 4%, respectively, in the placebo group (11). Short- and long-term infliximab therapy is generally well tolerated; however, clinicians must be vigilant for the occurrence of serious events, including serum sickness-like reaction, opportunistic infections and sepsis, and autoimmune disorders (12, 13). Repeated administrations of infliximab every eight weeks were well tolerated and produced suppression of the disease activity in our patient. The only side effect of the therapy was bacterial pneumonia which was responsive to standard antibiotic treatment.

In conclusion, the optimal therapy of CD is not established, and different opinions exist for the management of the disease. Infliximab appears to be an effective and safe therapy for pediatric patients with CD.

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