

Efficacy of Early Infliximab Treatment for Pediatric Crohn's Disease: A Three-year Follow-up

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Purpose: To investigate the efficacy of early infliximab use and to follow the progress of pediatric cases of Crohn's disease for 3 years.

Methods: We reviewed the medical records of 28 pediatric patients who had been treated with infliximab for Crohn's disease. Eighteen patients (the 'top-down' group) received infliximab and azathioprine for induction and maintenance therapy for the first year, and then were treated with azathioprine for 2 additional years. Ten patients who were refractory to conventional therapy were categorized in the 'step-up' group. All patients were followed for at least 36 months. Treatment efficacy was assessed by the relapse rate using the pediatric Crohn's disease activity index (PCDAI) score in each group at 12, 24, and 36 months. Blood samples were available from 10 patients, and were used to assess antibody to infliximab (ATI).

Results: The relapse rate in 'top-down' group was lower than that in 'step-up' group at 1, 2, and 3 years. But, just the relapse rate at the 2 years was significantly different. At 3 years, the relapse rate according to different characteristic variables (sex, age at diagnosis, involvement, PCDAI at diagnosis) was not significantly different. Only one patient treated with infliximab had an adverse event, consisting of dyspnea and tachycardia. ATI was not detected in the blood samples from 10 patients.

Conclusion: Early induction with infliximab at diagnosis ('top-down' therapy) is effective for reducing the relapse rate compared to conventional therapies in pediatric Crohn's disease possibly for up to 3 years. (**Pediatr Gastroenterol Hepatol Nutr 2012; 15: 243~249**)

Key Words: Infliximab, Pediatric Crohn's disease, Relapse rate, Top-down treatment

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory

disorder involving any part of the gastrointestinal tract, characterized by relapsing and remitting episode [1-3]. The etiology is incompletely under-

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stood, although the common opinion is that the disease arises from a disordered immune response to the gut contents in genetically predisposed individuals [4]. There is no known cure for CD. Therefore, the goal of treatment is to minimize change to the underlying course of CD and to restore normal bowel function [5-7].

Infliximab is a mouse-human chimeric antibody against tumor necrosis factor α , and has proven to be effective in active CD for both induction and maintenance therapy [8-10]. Infliximab is more effective in children than in adults [11,12]. Since receiving United States Food and Drug Administration approval for pediatric use in May 2006, infliximab has been widely used in pediatric patients with CD [13].

The efficacy of infliximab suggests that, rather than a progressive course of treatment, early intense induction may reduce complications associated with conventional treatment and improve quality of life. Intensive early therapy with infliximab is known as the 'top-down' strategy [14].

Several studies have compared the effects of 'top-down' and 'step-up' strategies in children [14-16]. The 'top-down' strategy was more effective than conventional management for induction of remission and initiation of intensive treatment early in the course of the disease resulted in better outcomes. However, there have been no reports comparing the long-term duration of efficacy of 'top-down' and 'step-up' treatments in pediatric patients with CD.

The purpose of this study was to evaluate the efficacy of the 'top-down' strategy compared to the 'step-up' strategy at 1, 2, and 3 years of follow-up in pediatric patients with CD.

MATERIALS AND METHODS

Patients

We included 28 patients who were diagnosed with CD, and had been followed for at least 36 months, at the Samsung Medical Center between March 1998 and January 2009. The patients were

given infliximab to treat conventional therapy-resistant CD and severe active CD for induction of remission were identified. A retrospective chart analysis was conducted. Biopsies were obtained by endoscopy in all eligible patients. CD was diagnosed in accordance with the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition-Porto criteria [17]. The efficacy of treatment was assessed by comparing the pediatric Crohn's disease activity index (PCDAI) scores. Infectious diseases, such as tuberculosis, were ruled out by taking a detailed family history, reviewing imaging studies that had been performed, and confirming the presence of a negative, purified-protein derivative test result with a negative PCR hybridization for *Mycobacterium tuberculosis* on biopsy tissue. The study was approved by the institutional review board of our institution (2012-04-051).

Study design

Enrolled patients were divided into two groups according to the treatment regimen. Ten patients refractory to conventional therapy, including eight with steroid-resistant CD and two with steroid dependent CD, were included in the 'step-up' group for infliximab treatment. Eighteen patients with moderate-to-severe CD were assigned to the 'top-down' group. In the 'step-up' group, oral corticosteroids (prednisolone, 1-2 mg/kg/day) were used for induction therapy. Mesalamine (50-80 mg/kg/day) or azathioprine (2-3 mg/kg/day) was provided for the conventional treatment as maintenance therapy. Infliximab (5 mg/kg) was administered by intravenous infusion at weeks 0, 2, and 6 in combination with daily azathioprine, and this course was repeated every 8 weeks for 10-12 months thereafter.

The 'top-down' group received infliximab and azathioprine for induction and maintenance therapy for the first year, and were treated with azathioprine after 2 years. The group treated with early infliximab had not been previously treated with other medications, such as corticosteroids or immunomodulators. All patients were followed for

at least 36 months.

Relapse rate

We defined disease remission as a PCDAI score of less than 10 points and relapse as a score greater than 10 points [18]. The relapse rate was defined as the rate of the presence of relapse, more than once, after a remission was achieved with treatment. Moderate to severe disease was defined as having a score greater than 30 points. The two groups were compared with regard to baseline characteristics, adverse events, clinical status (including the PCDAI score) and relapse rates at 1, 2, and 3 years.

Adverse events

Adverse events and laboratory results were investigated to identify potential side effects. Patients treated with mesalamine underwent evaluations for hypersensitivity, rash, alopecia, anorexia, headache, elevated liver enzymes, and pancreatitis. For azathioprine, patients were evaluated for pancytopenia, pancreatitis, hepatotoxicity, rash, alopecia, anorexia, and arthralgia. Patients receiving infliximab were assessed for anaphylaxis, dyspnea, rash, headache, nausea, elevated liver enzymes, pancreatitis, pancytopenia, and serious infections. Evaluation of well-known adverse effects of prednisolone was not included in the analysis.

Measurement of antibody to infliximab

Peripheral blood samples of 5 mL each were collected from patients with at least three previous infliximab infusions. A commercially available enzyme-linked immunosorbent assay (ELISA) kit (Matriks Biotek Laboratories, Ankara, Turkey) was used to detect antibody to infliximab (ATI). The assay was based on a highly specific double antigen binding assay principle. In this procedure, the specific antibody in serum, namely ATI, binds to the infliximab-coated well with one of its Fab arms and also binds to the biotinylated infliximab with the aid of its other Fab arm. The ELISA kit demonstrates the presence of ATI, and the in-

tensity of the color developed is proportional to the amount of specific antibody [19].

Statistical methods

Analyses comparing the study groups were performed using the χ^2 test for variables. Fisher's exact test was used to compare each of the measurements. Logistic regression analysis was used to compensate for difference in baseline characteristics. A $p < 0.05$ was regarded as statistically significant.

RESULTS

Baseline characteristics

The study population at diagnosis included 24 males (85.7%) and four females (14.3%) with a mean age of 12.9 ± 3.9 years. The location of disease was the terminal ileum in two patients (7.1%), the colon in four patients (14.2%) and the ileocolon in 24 patients (78.6%). The average total number of infliximab infusions for each patient was 10.3 ± 3.1 . The mean PCDAI score at initial diagnosis was 40.5 ± 11.3 (Table 1).

Difference in baseline characteristics of two groups

PCDAI scores at initial diagnosis, before infliximab treatment, and the total number of infliximab infusions were not significantly different the two groups. The age at diagnosis was 10.2 ± 5.4 years in the 'step-up' group and 14.4 ± 1.3 years in

Table 1. Baseline Characteristics of Patients

Characteristic	Value
Number of patients	28
Gender (male/female)	24/4
Total number of infliximab infusions	10.8 ± 3.1
Disease location	
Small intestine	2
Colon	4
Small and large bowel	24
PCDAI at diagnosis	40.5 ± 11.3

Values are presented as number or mean \pm standard deviation. PCDAI: pediatric Crohn's disease activity index.

Table 2. Difference in Baseline Characteristics of Patients in Each Treatment Group

Characteristic	Step-up group	Top-down group	<i>p</i> -value
Number of patients	10	18	
Gender (male/female)	16/2	8/2	0.602
Median age (yr)	10.2±5.4	14.4±1.3	0.010
PCDAI at diagnosis	41.5±12.5	39.9±10.9	0.530
Duration from the initial diagnosis to infliximab infusion (week)	49.6±5.2	1.8±2.4	0.001
Total number of infliximab fusions	9.2±3.0	10.8±3.1	0.204
PCDAI at prior 1st infliximab infusion	30.5±14.9	40.4±10.2	0.069

Values are presented as number or mean±standard deviation. PCDAI: pediatric Crohn’s disease activity index.

the ‘top-down’ group. The duration from the initial diagnosis to infliximab infusion was 49.6±5.2 weeks and 1.8±2.4 weeks for the ‘step up’ and ‘top-down’ groups, respectively (Table 2).

Relapse rate

The relapse rate of two sex groups was not significant different (*p*=0.295); 66.7% (16 of 24 patients) for male patients and 100% (four of four patients) for female patients. There was no significant difference in the relapse rate between the different age groups (*p*=0.295); 100% (four of four patients) for patients less than 12 years of age and 66.7% (16 of 24 patients) for those more than 12 years of age. The relapse rate in patients who only had colon involvement was 50.0% (two of four patients). The relapse rate in patients with terminal ileum only involvement was 100% (two of two patients), and for patients with ileocolonic involvement the relapse rate was 72.7% (16 of 22 patients). There was no difference in the relapse rate between patients with mild disease, with a PCDAI score less than 30 points at diagnosis (two of four patients, 50%), and moderate to severe disease, with a PCDAI score more than 30 points (19 of 24 patients, 64.3%) (Table 3).

The baseline characteristics of age and duration from the initial diagnosis to infliximab infusion (week) were significantly different between the two groups. These variables were confounding factors, and the relapse rate of the ‘top-down’ group was lower than that of the ‘step-up’ group.

Table 3. Relapse Rate at 3 Years by Patient Characteristics

Characteristic	N (%)	<i>p</i> -value
Age at diagnosis		0.295
≥12 years (n=4)	4 (100)	
<12 years (n=24)	16 (66.7)	
Gender		0.295
Male	16 (66.7)	
Female	4 (100)	
Disease location		0.589
Small intestine	2 (100)	
Colon	2 (50)	
Small and large bowel	16 (72.7)	
PCDAI at diagnosis		0.555
≥30 (n=24)	19 (64.3)	
<30 (n=4)	2 (50)	

PCDAI: pediatric Crohn’s disease activity index.

The relapse rate at 1 year was 16.7% in ‘top-down’ group (3 out of 18 patients), 50% in ‘step-up’ group (five of 10 patients). At 1-year, the absolute difference between two groups was 33.3%. There was not a significant difference between the groups (*p*=0.091). At the 2-year follow-up, the relapse rate in ‘top-down’ group was 50% (9 out of 18 patients) and 90% in the ‘step-up’ group (nine of 10 patients). At 2 years, the absolute difference between two groups was 40%. There was a significant difference between the groups (*p*=0.048). At the 3-year follow-up, the relapse rate of each group was 61.1% and 90%. There was no significant difference (*p*=0.194) (Fig. 1).

Antibody to infliximab

Ten patients were checked for the presence of

ATI. We divided the patients into two groups according to PCDAI at sampling time: 'maintained response to infliximab' and 'loss of response to infliximab'. ATI was not detected in either group. Table 4 summarized ATI detection results.

Adverse events

Two patients treated with mesalamine had anorexia. Eleven patients treated with azathioprine experienced adverse events (leukopenia in nine and pancreatitis in two). For patients treated with infliximab, only one patient in the 'step-up' group had an adverse event, consisting of dyspnea and tachycardia that occurred after the third infusion.

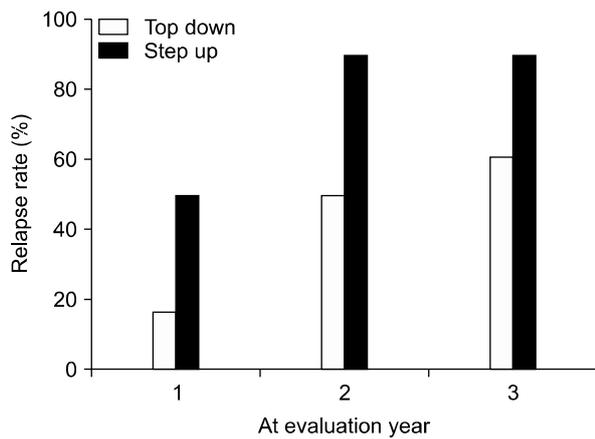


Fig. 1. Relapse rate at 1, 2 and 3 years.

DISCUSSION

The potential of infliximab, not only to induce but also to maintain remission, has been well studied in adult and pediatric CD cohorts [16,20,21]. Similarly, this study found that the early use of infliximab was more effective for the treatment of pediatric patients with moderate to severe CD than conventional 'step-up' therapy for 3 years. The mechanism(s) by which the 'top-down' strategy yields superior results when compared to 'step-up' treatment in regard to remission rates remains unclear. However, it is suggested that the patients in the 'step-up' group had a much longer duration of disease and that they were exposed to more extensive tissue damage [14]. Van Limbergen et al. [20] reported that infliximab treatment early in the disease course may avoid the irreversible tissue damage often found in the later stages of CD.

Colombel et al. [22] reported that infliximab combination therapy was more effective in inducing steroid-free clinical remission than infliximab monotherapy ($p=0.022$). These effects were sustained through to 50 weeks. Similarly, although presently the relapse rate ('top-down' group was 50% and 90% in the 'step-up' group) of 3 years was not significant ($p=0.194$), and was superior than the 'step-up' group.

Infliximab treatment appears to be well tol-

Table 4. Baseline Characteristics of Patients and Results of Antibody to Infliximab Detection Test

	PCDAI at diagnosis	PCDAI at sampling time	Previous infliximab infusions	ATI detection	Remission at 3 years
Loss of response					
1	52.5	12.5	10	No	No
2	32.5	12.5	8	No	No
3	47.5	22.5	5	No	No
4	40	35	8	No	No
Maintained response					
5	35	0	4	No	Yes
6	40	10	10	No	No
7	37.5	2.5	6	No	Yes
8	60	2.5	5	No	No
9	50	15	4	No	Yes
10	40	5	7	No	No

PCDAI: pediatric Crohn's disease activity index, ATI: antibody to infliximab.

erated [23], but anaphylactic reactions and symptoms caused by immunosuppression, such as upper respiratory tract infections, herpes zoster activation, severe acute bacterial infections and an increased risk of tuberculosis, have all been described following treatment with infliximab [23,24]. One of the major concerns, despite its wide use, is potential development of ATI, which in turn may interfere with infliximab efficacy as mainly judged by observing the relapse of signs and symptoms of disease, and necessitates dose-escalation or potentially ending treatment [19]. After repeated dosing is performed, some patients have human antibodies to chimeric tumor necrosis factor-alpha antibodies [25,26]. Although ATI were evaluated in the current study, there were no significant findings. In our study, ATI measurement was performed in a small number of patients, but currently is being performed on all other patients.

There were several limitations of this study. This was a single center study with a small number of patients who were reviewed retrospectively. As an open trial, the physicians and patients knew the treatment regimen, which could have biased the assessment of treatment efficacy. Future studies addressing long-term follow-up are needed to determine the safety and efficacy of infliximab treatment.

To our knowledge, this is the first study reported in Korea comparing the efficacies of 'top-down' infliximab treatment and 'step-up' treatment for pediatric CD over a 3-year period [10,27,28]. Although, relapse rate at 1 and 3 years was not significantly different, the relapse rate of the 'top-down' group was lower than that of the 'step-up' group.

In conclusion, the results of this study show that early and intensive treatment of pediatric CD patients with infliximab is more effective for maintaining remission and possibly for reducing flares.

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