Original Article

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Adalimumab Treatment in Pediatric-Onset Crohn's Disease Patients after Infliximab Failure: A Single Center Study

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Purpose: We aimed to investigate the efficacy and safety of adalimumab in pediatric-onset Crohn's disease patients who had failed treatment with infliximab.

Methods: In this retrospective study, patients included were those who had been diagnosed with Crohn's disease before 18 years old, and had received treatment with adalimumab after infliximab failure. The efficacy of adalimumab treatment was investigated at 1 month and 1 year, and adverse events that had occurred during treatment with adalimumab were explored.

Results: Ten patients were included in this study. The median duration from diagnosis to adalimumab treatment was 5.5 years (range: 2.4-7.9 years). At 1 month after adalimumab initiation, 80% (8/10) of patients showed clinical response, and 40% (4/10) achieved clinical remission. At 1 year, 71% (5/7) of patients showed clinical response, and 43% (3/7) were under clinical remission. Among the total included patients, 5 patients (50%) showed clinical response at 1 year. Primary non-response to adalimumab was observed in 2 patients (20%), and secondary failure to adalimumab was observed in 3 patients (30%) during 1 year treatment with adalimumab. No serious adverse event had occurred during adalimumab treatment.

Conclusion: Adalimumab was effective for 1 year without serious adverse events in half of pediatric-onset Crohn's disease patients who had failed treatment with infliximab.

Key Words: Pediatric Crohn's disease, Adalimumab, Antibody to infliximab

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease that can affect the entire gastrointestinal tract, which is characterized by periods of clinical remission and relapse [1]. The disease course is usually progressive and half of affected patients are known to experience complications such as strictures and fistulas leading to persisting and refractory symptoms, impaired quality of life and surgery [2,3]. With the introduction of infliximab (IFX), a chimeric monoclonal antibody that binds with high

specificity and affinity to tumor necrosis factor-alpha (TNF-α), a large majority of CD patients in diverse age groups refractory to conventional treatments have benefited from its use [4-6]. However, disease relapse due to loss of response (LOR) to IFX is another problem that clinicians face during treatment, requiring adjustments of dose or duration, or a switch to an alternative anti-TNF-α agent, such as adalimumab (ADA) [7].

ADA is a fully humanized monoclonal antibody to TNF-α, that is effective in inducing and maintaining clinical remission in luminal CD patients of moderate-to-severe degree [8-11]. In Korea, ADA has been approved for usage in 2007 in patients of 18 years or more. As its usage in the pediatric population in Korea has been approved just recently in 2015, there is currently no data on the efficacy and safety of ADA in pediatric CD patients of Korea. Fortunately, we have experienced some pediatric-onset CD patients who had received ADA after 18 years of age. Therefore, in this retrospective study we aimed to investigate the efficacy and safety of ADA treatment in patients with pediatric-onset CD who had received ADA after 18 years of age following failure to IFX treatment.

MATERIALS AND METHODS

This retrospective study was conducted at the Department of Pediatrics at Samsung Medical Center between January 2010 and December 2014. Patients included were those who had been diagnosed with CD before 18 years old, and had received treatment with ADA after IFX failure. CD was diagnosed in accordance with the revised Porto criteria of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition, and patients of indeterminate type inflammatory bowel disease were excluded [12]. Disease classification and behavior was based on the Paris classification [13].

Data including sex, age, disease classification, past medication and CD related surgery history prior to ADA treatment, disease activity scores of Crohn's disease activity index (CDAI) calculated at each visit during ADA treatment, laboratory tests including complete blood cell counts with differential counts, chemistry profiles, and C-reactive protein (CRP), concomitant medication and adverse events during ADA treatment were obtained from electronic medical charts of the hospital. Antibody to infliximab (ATI) levels were obtained from the electronic database of an ongoing cohort at our center, in which ATIs had been measured from sera obtained at the point of IFX cessation using an enzyme-linked immunosorbent assay kit (Matriks Biotek Laboratories, Ankara, Turkey) [14].

The efficacy of ADA treatment was determined by clinical response and clinical remission rates evaluated at 1 month and 1 year. As all patients included in this study were 18 years or more, definitions for clinical outcomes were based on the CDAI. Clinical response was defined as a reduction in CDAI score $\geq$ 70 points from baseline, and clinical remission was defined as a reduction in CDAI < 150 points. Primary non-response or primary failure was defined at 1 month as a CDAI decrease of < 70 points compared with baseline. Secondary LOR was defined as a CDAI decrease of < 70 points compared with baseline during 2 consecutive visits among patients who had achieved clinical response at 1 month. Secondary failure was defined as a status of maintaining LOR despite interval shortening to 1 week [10,15].

Clinical remission rates at 1 year were compared between groups divided according to ATI status at IFX cessation, and according to combined immunosuppression status during ADA by using the Fisher's exact test on IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). The p-value for statistical significance was defined as $p < 0.05$. This study was approved by the Institutional Review Board of Samsung Medical Center (IRB no. 2015-04-123).

RESULTS

Patient characteristics

Ten patients were included in this retrospective study. All of the patients were diagnosed before 18

Table 1. Patient Information on Baseline Characteristics, Treatment Course, and Adverse Events during Adalimumab Treatment

Variable	Patient number									
	1	2	3	4	5	6	7	8	9	10
Baseline characteristics										
Sex	M	M	M	M	F	M	F	M	F	F
Age at diagnosis (yr)	13.5	11.3	14.1	16.9	17.8	13.2	13.9	14.6	15.0	13.2
Age at baseline ADA (yr)	19.0	19.2	19.5	19.3	21.7	19.0	18.4	20.1	21.0	20.6
Disease duration (yr)	5.5	7.9	5.4	2.4	3.8	5.9	3.4	5.4	6.0	7.4
Disease location*	L3+L4ab	L3+L4b	L3+L4b	L3	L2	L3+L4b	L3	L3+L4ab	L3	L3+L4a
Disease behavior at diagnosis	B1p	B1p	B1p	B1	B1p	B1p	B1	B1	B1p	B2
Disease behavior at baseline ADA	B2p	B2p	B1p	B1	B1p	B2p	B2	B1	B1p	B2
Growth delay before baseline ADA	G1	G1	G1	G0	G0	G0	G0	G1	G0	G0
Duration of IFX treatment (yr)	1.0	1.8	3.5	2.2	3.7	3.0	3.3	2.6	6.0	4.6
ATI status at IFX cessation	Negative	Positive	Negative	Positive	Negative	Positive	Positive	Negative	Negative	Positive
Concomitant CS at baseline ADA	Yes	Yes	No	No	No	Yes	No	No	No	No
Concomitant AZA at baseline ADA	Yes	Yes	No	No	Yes	Yes	No	No	Yes	Yes
CDAI at baseline ADA	443	223	316	231	262	223	276	299	266	299
CRP at baseline ADA (mg/dL)	8.91	4.43	3.34	0.5	0.82	5.06	2.47	4.5	1.53	0.81
Treatment course										
Clinical status at 1 month	1° failure	Remission	Response	Remission	1° failure	Response	Response	Remission	Response	Remission
Dose intensification	N/A	No	Yes	Yes	N/A	Yes	Yes	No	Yes	No
ADA cessation during the first year	Yes	No	No	No	Yes	Yes (2° failure)	No	No	No	No
Clinical status at 1 year	N/A	Remission	2° failure	Response	N/A	N/A	Response	Remission	2° failure	Remission
Concomitant CS at 1 year	N/A	No	Yes	No	N/A	N/A	No	No	No	No
Concomitant AZA at 1 year	N/A	Yes	No	No	N/A	N/A	No	No	Yes	Yes
CDAI at 1 year	N/A	39	263	122	N/A	N/A	170	68	228	18
CRP at 1 year (mg/dL)	N/A	0.23	3.33	0.62	N/A	N/A	1.58	0.21	3.62	0.03
Treatment duration with ADA (mo)	21	2	3	7	12	8	13	18	14	16
Continuously under ADA at latest follow up	Yes	No	No	No	No	No	No	Yes	No	Yes
Adverse events	None	URI	Arthralgia, acne	None	None	None	Injection site pain	None	Arthralgia, injection site pain	None

M: male, F: female, ADA: adalimumab, L2: colonic disease, L3: ileocolonic disease, L4a: upper disease proximal to ligament of Treitz, L4b: upper disease distal to the ligament of Treitz and proximal to the distal 1/3 ileum, L4ab: upper disease involvement in both L4a and L4b, B1: nonstricturing, nonpenetrating behavior, B1p: nonstricturing, nonpenetrating behavior with perianal disease, B2: stricturing behavior, B2p: stricturing behavior with perianal disease, G0: no evidence of growth delay, G1: growth delay, IFX: infliximab, ATI: antibody to infliximab, CS: corticosteroid, AZA: azathioprine, CDAI: Crohn's disease activity index, CRP: C-reactive protein, N/A: not applicable, URI: upper respiratory infection.

years of age, and all were 18 years or over at baseline ADA infusion. The median duration of IFX treatment before ADA was 3 years (range: 1-6 years). All patients had failed IFX due to secondary LOR and ATI was positive in 5 patients (50%). All patients had prior medication histories with azathioprine (AZA), mesalazine, and exclusive enteral nutrition, respectively. Corticosteroids had been previously administered in all patients except patient number 8, and tacrolimus had been administered in only patient number 3. Family history of inflammatory bowel disease was positive in patient number 4, whose father was a CD patient. Family histories of other relevant diseases such as malignancies, tuberculosis, or autoimmune diseases were all negative. Data regarding baseline characteristics, treatment course, and adverse events during ADA treatment are described for each subject in Table 1.

Clinical course and efficacy during adalimumab treatment

The median follow-up period was 12.5 months (range: 2-21 months). ADA was administered at doses of 160 mg on the first infusion, and 80 mg on the second infusion 2 weeks later. Thereafter, 40 mg of ADA were given every 2 weeks. At 1 month, 80% (8/10) of patients showed clinical response, and 40% (4/10) achieved clinical remission. Two patients were primary non-responders to ADA. Symptoms and laboratory markers worsened in one patient leading to discontinuation of ADA at 2 months, and one patient required bowel surgery at 2.5 months. Among the primary responders, 50% (4/8) required interval shortening to 1 week due to secondary LOR. One patient stopped ADA due to secondary failure at 6 months.

At 1 year from baseline ADA, 7 patients were continuously under ADA. Clinical response was observed in 71% (5/7), clinical remission in 43% (3/7), and secondary failure was observed in 29% (2/7). Among the total study patients, 50% (5/10) showed clinical response, 30% (3/10) were under clinical remission, and 50% (5/10) had failed ADA treatment during the first year (Fig. 1). For the 3 patients who were under clinical remission throughout 1 year, median CDAI was 39 (range: 39-68), and median CRP was 0.21 mg/dL (range: 0.03-0.23 mg/dL).

At ADA initiation, 3 patients (30%) were on corticosteroids, and 6 patients (60%) received combined immunosuppression with AZA. Among the 7 pa-
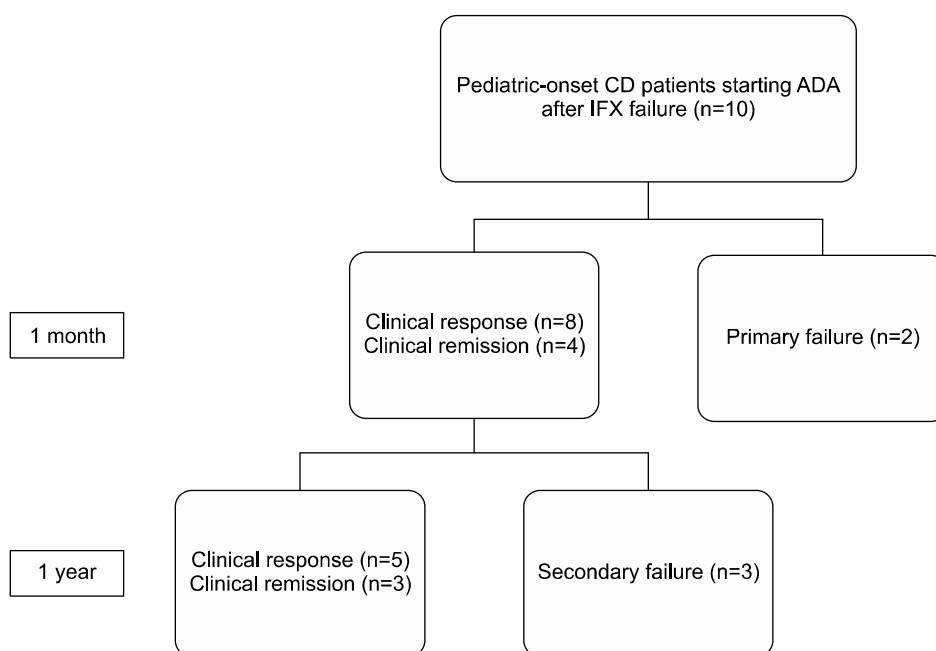

Fig. 1. Schematic outline of clinical outcome during treatment with adalimumab. CD: Crohn's disease, ADA: adalimumab, IFX: infliximab.
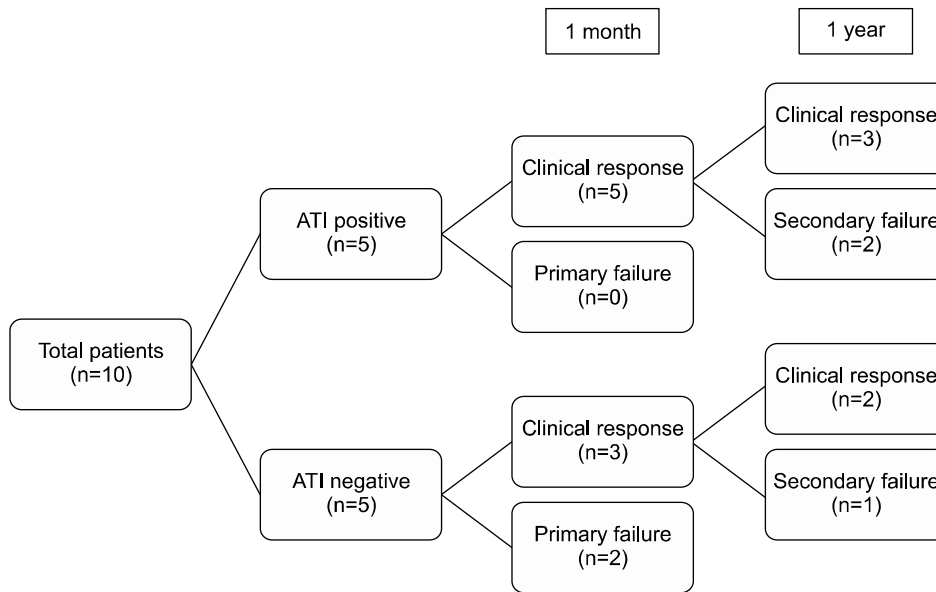
Fig. 2. Clinical outcome between groups divided according to antibody to infliximab (ATI) status at infliximab cessation.

tients who were continuously on ADA at 1 year, 1 patient (14%) was receiving corticosteroids, and 3 patients (43%) were receiving combined immunosuppression with AZA.

The clinical outcome of the patients, divided into groups according to ATI status at IFX cessation, is outlined in Fig. 2. Comparison of clinical remission rates at 1 year according to ATI status at IFX cessation revealed rates of 40% (2/5) for those who were positive for ATI, and 20% (1/5) for those who were negative for ATI ($p=0.583$). Comparison of clinical remission rates at 1 year according to combined immunosuppression status during ADA revealed rates of 33% (2/6) for those who received concomitant AZA, and 25% (1/4) for those who received only monotherapy ($p=1.000$).

Safety of adalimumab treatment

Four adverse events occurred in 3 patients (30%) during treatment with ADA. The adverse events were injection site pain and redness in 2 patients, upper respiratory infection in 1 patient, and acne in 1 patient. However, no serious adverse event such as anaphylaxis or systemic infections leading to discontinuation of ADA occurred.

DISCUSSION

This is the first study in Korea to evaluate the efficacy and safety of ADA treatment in pediatric-onset CD patients who failed IFX treatment. ADA was effective for inducing remission in 40% at 1 month and maintaining remission in 30% at 1 year in moderate-to-severe CD patients of pediatric-onset who had failed treatment with IFX. Overall, half of patients who had failed IFX benefited from treatment with ADA at 1 year without any serious adverse events.

The results of our study showed similar rates of clinical response and remission compared to previous studies in pediatric CD patients receiving ADA. According to the IMAgINE 1 study, 82.4% had responded to induction and 27.7% were in clinical remission at week 4 [11]. According to several retrospective studies based on clinical data from real-life practice, ADA was capable of inducing remission in 61-64% within a median of 2.4-3.3 months in IFX refractory patients, and among those who were continuously on ADA at 1 year, 41-53% were under remission [16-18]. However, overall ADA failure rate at 1 year was 50% in our study, showing higher rates compared to previous studies of 15-28% during the first year of treatment with ADA [16-18]. The long

disease duration (median: 5.5 years) and high percentage of patients with stricturing type behavior (50%) in our study could explain this worse outcome in our study compared to previous ones. Meanwhile, another recent retrospective study has reported similar results with our study demonstrating a cumulative probability of failure up to 55% at 1 year [19].

No significant differences in clinical remission rates were observed between groups divided according to ATI status at IFX cessation in our study, although the clinical remission rates were higher in patients with ATIs. Our results correlate with the results of the study by Cozijnsen et al. [18]. According to their study, higher remission rates and lower failure rates were observed in patients with ATIs compared to those without ATIs at the time of IFX failure, although statistical significances were not observed. The clinical remission rates were 81% (17/21) vs. 53% (9/17) for patients with ATIs vs. without ATIs ($p=0.09$), and failure rates were 19% (4/21) vs. 41% (7/17) for patients with ATIs vs. without ATIs ($p=0.13$; hazard ratio, 0.37; 95% confidence interval, 0.11-1.23), respectively [18]. Meanwhile, according to a study in adult CD patients switching treatment to ADA after LOR to IFX, ATIs were associated with development of de novo antibodies to ADA (ATAs) and consequent therapeutic failure [20]. Patients with previous ATIs were significantly more likely to develop ATAs (33%) compared to those without ATIs (0%) ($p=0.04$), and the presence of ATAs increased the risk of secondary ADA treatment failure with an odds ratio of 28 (3-248) ($p=0.001$) [20]. Further large-scale prospective studies are required to clarify this discrepancy between studies.

No significant differences in clinical remission rates were observed between groups divided according to combined immunosuppression status during ADA in our study. Our results correlate with the results of previous trials from adults, in which no beneficial effects of combination therapy were observed compared with ADA monotherapy regarding clinical response or remission in luminal CD [8-10,21]. Moreover, results from a recent meta-analysis concluded that the continued use of immunomodulator therapy after starting anti-TNF therapy is no more effective than monotherapy in inducing or maintaining response or remission [22]. As serious adverse events, such as non-melanoma skin cancer and other malignancies, have been reported to be associated with co-administration of immunomodulators during ADA treatment, combination therapy during ADA should be considered individually by weighing its risk against potential benefits [23].

The major limitation of this study is the small number of included patients. Therefore, there were limitations in performing statistical analysis and deriving significant results. Another limitation of this study is the age of the patients when ADA was first initiated. All patients had received ADA after 18 years of age because ADA was not approved for usage in pediatric CD patients until May, 2015 in Korea. Therefore, no patient was under 18 years when ADA was first administered, although all were diagnosed before 18 years of age. Another limitation is that ATAs and ADA trough levels were not investigated during ADA treatment.

In conclusion, ADA was effective for 1 year without serious adverse events in half of pediatric-onset CD patients who had failed IFX treatment. Further large-scale studies in the pediatric population are required in the future, including data regarding ATAs and ADA trough levels.

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