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Original Article

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Clinical Course of Infliximab Treatment in Korean Pediatric Ulcerative Colitis Patients: A Single Center Experience

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Purpose: Infliximab (IFX) is considered safe and effective for the treatment of ulcerative colitis (UC) in both adults and children. The aim of this study was to evaluate the short- and long-term clinical course of IFX in Korean children with UC.

Methods: Pediatric patients with UC who had received IFX infusions between November 2007 and May 2013 at Samsung Medical Center were retrospectively investigated. The clinical efficacy of IFX treatment was evaluated at 8 weeks (short term) and 54 weeks (long term) after the initiation of IFX treatment using the Pediatric Ulcerative Colitis Activity Index (PUCAI). The degree of response to IFX treatment was defined as complete response (PUCAI score=0), partial response (decrement of PUCAI score $\geq$20 points), and non-response (decrement of PUCAI score $<$20 points). Adverse events associated with IFX treatment were also investigated.

Results: Eleven pediatric patients with moderate to severe UC had received IFX. The remission rate after IFX treatment was 46% (5/11) and 82% (9/11) at 8 weeks and 54 weeks after IFX treatment, respectively. All patients who were steroid-dependent before treatment with IFX achieved remission at 54 weeks and were able to stop treatment with corticosteroids, while all steroid-refractory patients failed to achieve remission at 54 weeks after treatment with IFX.

Conclusion: Response to IFX treatment after 8 weeks may predict a favorable long-term response to IFX treatment in Korean pediatric UC patients.

Key Words: Inflammatory bowel diseases, Ulcerative colitis, Infliximab, Child, Korea

INTRODUCTION

Although ulcerative colitis (UC) may affect people of any age, its occurrence peaks in late adolescence, with 20% of patients presenting before the age of 20 years [1]. UC has classically been managed with anti-inflammatory drugs containing 5-aminosalicylic acid (5-ASA) and with corticosteroids, depending on

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topographic extension and on the severity of the colonic inflammation. For patients with acute moderate or severe symptoms of UC who have been unresponsive to corticosteroid therapy, medical management has included 6-mercaptopurine (6-MP) or azathioprine and cyclosporine [2-7].

Infliximab (IFX), an anti-tumor necrosis factor-α monoclonal antibody, is considered safe and effective for the treatment of UC in adults and Crohn's disease in children [8,9]. Some preliminary studies have also indicated that the response to IFX therapy is similar in pediatric and adult UC patients, and that IFX is safe and effective in pediatric patients with moderate to severely active UC who did not respond to conventional therapy [10-12].

On the other hand, IFX treatment in Korean pediatric UC patients has been limited due to national insurance coverage matters in Korea. It has been only recently that IFX was approved for national insurance coverage among children in this country. Consequently, there are no data regarding the clinical course of IFX in Korean children. Therefore, this aim of this study was to evaluate the clinical course of IFX in Korean pediatric patients with UC.

MATERIALS AND METHODS

Pediatric patients with UC who had received IFX infusions between November 2007 and May 2013 at Samsung Medical Center were retrospectively investigated. Medical charts were reviewed for sex, age at diagnosis, age at first IFX infusion, duration of disease at first infusion, number of IFX infusions, extent of disease, indications for IFX infusion, concurrent medications, clinical course during IFX treatment, and acute and delayed adverse events associated with IFX treatment.

Indications for IFX therapy were classified as treatment of fulminant UC unresponsive to steroids or treatment of acute exacerbations. Fulminant UC was defined as a severe attack of UC not responding to treatment with corticosteroids, and urgently requiring intensive in-hospital treatment. Acute exacerbation was defined as a relapse or a case in which the Pediatric Ulcerative Colitis Activity Index (PUCAI) score acutely increased by more than 50% of the baseline value. IFX (5 mg/kg) was administered by intravenous infusion at weeks 0, 2, and 6, in combination with daily azathioprine or mesalazine, and this course was repeated every 8 weeks.

Clinical response was evaluated according to the PUCAI score. Patients with complete resolution of symptoms (PUCAI score=0) were classified as complete responders (remission), while patients with a reduction of symptoms (a decrease in PUCAI score of more than 20 points) were classified as partial responders. Non-responders were defined as patients who exhibited no change or a decrease of less than 20 points in the PUCAI score. Regarding the timing of response assessment, short-term response was evaluated at 8 weeks after the initial IFX infusion, and long-term response was assessed at 54 weeks after the initial infusion. Patients were considered to be steroid-refractory if they had no response to at least 40-60 mg/day of prednisolone for at least 7 days, and as steroid-dependent if they responded to 1 mg/kg/day of prednisolone but redeveloped symptoms when doses were tapered to <0.5 mg/kg/day.

This study was approved by the institutional review board of Samsung Medical Center.

RESULTS

Baseline characteristics

The study population at diagnosis included six males (55%) and five females (45%). Median age at diagnosis was 14 years, ranging from 12.2 to 15.7 years. Median age at first IFX was 15.4 years (interquartile range [IQR] 14.2-16.7), and the median disease duration prior to IFX treatment was 0.8 years (IQR 0.55-2.2). The median follow-up period from first IFX infusion was 27 months (IQR 19-37.5). The extent of the disease was pancolitis in eight patients (73%), left-sided colitis in two patients (18%), and proctitis in one patient (9%).

Two left-sided colitis patients and one proctitis patient whose symptoms were aggravated and PUCAI

scores were high had IFX treatment. Surgery was also considered for non-responders in case IFX did not show a sufficient effect.

The median number of IFX infusions was 10 (IQR 6.5-11.5). All patients had been taking concurrent medications such as corticosteroids, mesalazine, or azathioprine. Six patients had taken oral corticosteroids for more than 7 days, 10 had been taking azathioprine, and all patients had been taking mesalazine. Indications for IFX infusion were fulminant UC in two patients (18%), who were both steroid-resistant, and acute exacerbation in nine patients (82%), who were all steroid-dependent (Table 1).

Table 1. Patient Demographics

Characteristic	Value
Total number of patients	11
Sex	
Male	6 (55)
Female	5 (45)
Age at diagnosis (yr)	14 (12.2-15.7)
Age at first infliximab dose (yr)	15.4 (14.2-16.7)
Disease duration prior infliximab (yr)	0.8 (0.55-2.2)
Follow-up from first infliximab infusion (mo)	27 (19-37.5)
Extent of disease	
Pancolitis	8 (73)
Left-sided	2 (18)
Proctitis	1 (9)
Reason for infliximab infusion	
Fulminant colitis	2 (18)
Non-fulminant colitis/acute exacerbation	9 (82)
Infliximab infusions (n)	10 (6.5-11.5)
Patients receiving other medications (n)	
Azathioprine	10 (91)
Corticosteroids	6 (55)
5-aminosalicylic acid	11 (100)
Cefotaxime	2 (18)
Metronidazole	1 (9)
PUCAI score at 1st infliximab infusion	70 (45-85)
PUCAI score after 3rd infliximab infusion	5 (0-30)
Steroid-refractory	2 (18)
Steroid-dependent	9 (82)
p-ANCA serology	
Positive	8 (73)
Negative	2 (18)
Not available	1 (9)

Values are presented as number only, number (%) or median (interquartile range).
PUCAI: Pediatric Ulcerative Colitis Activity Index.

Clinical course

The remission rates after IFX treatment were 46% (5/11) and 82% (9/11) at 8 weeks and 54 weeks after IFX treatment, respectively. Five patients showed complete resolution of symptoms (short-term responders), and five showed partial improvement of symptoms at 8 weeks after the first IFX infusion (short-term partial responders). One patient did not show a short-term response (short-term non-responder; Fig. 1).

During the follow-up period, all five short-term responders had remained in remission (long-term responders). Among the five short-term partial responders, four patients had achieved remission (long-term responders), while one fulminant UC patient received a total colectomy after 46 months from the first IFX infusion. This patient also had concurrent cytomegalovirus-colitis and treatments with IFX, steroid, and ganciclovir had been conducted. One short-term non-responder did not show a response to IFX, cyclosporine, or corticosteroid. This patient remained in a state of severe UC without operation under the treatment of mesalazine, maintaining PUCAI scores of 40 to 50. An operation was planned for this patient.

The two long-term non-responders were steroid-refractory. The median age at diagnosis was 14 years and the median disease duration was 0.9 years. The median total number of IFX infusions was 7.5. The two patients with fulminant UC were administered IFX in combination with azathioprine. The median PUCAI score at the first IFX infusion was 70 and that at the third IFX infusion was 50.

In the case of responders, the median age at diagnosis was 13.5 years and the median disease duration was 0.8 years. Eight of 9 responders were treated with IFX in combination with azathioprine. One responder did not receive azathioprine because of side effects (pancytopenia and hair loss). The median PUCAI score at first IFX infusion was 65 and that at the third IFX infusion was 0. No statistical differences in response were noted with regard to age at diagnosis, disease duration, or age at first IFX infusion.

In terms of the short-term response, all nine pa-

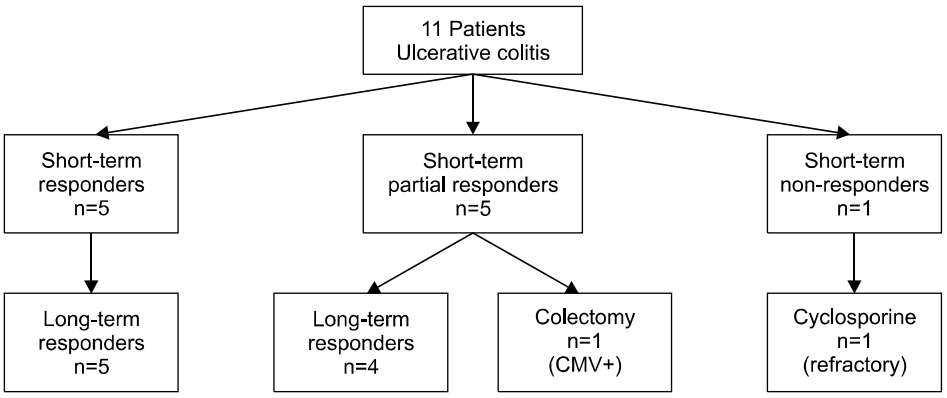

Fig. 1. Flow chart showing short- and long-term responses to infliximab. CMV: cytomegalovirus.

tients who were steroid-dependent before the present treatment responded to IFX (100%), whereas one of two steroid-refractory patients (50%) responded to IFX. In relation to the long-term response, all nine patients who were steroid-dependent before treatment with IFX achieved remission and became long-term responders (100%); they were ultimately able to stop corticosteroid treatment.

Three out of nine long-term responders showed mucosal healing, so they stopped IFX treatment and have remained in remission. Six of the nine patients continue to receive IFX as a maintenance treatment, and they are also in remission. On the other hand, Steroid-refractory patients (n=2) were unable to achieve remission at 54 weeks (long-term non-responders). In the five patients who stopped IFX (three long-term responders and two long-term non-responders), the median follow-up period from the last IFX infusion was 18.5 months (IQR 15.5-18.5).

Side effects

One patient had chest tightness and tachycardia during IFX infusion, which spontaneously resolved by decreasing the infusion rate. Thereafter, no similar adverse event associated with IFX infusion was observed in this patient. Neither acute nor delayed adverse events associated with IFX treatment were observed in the other subjects.

DISCUSSION

Current treatments for UC include 5-ASA compounds, antibiotics, immunomodulators, and corticosteroids, but the potential adverse effects of corticosteroids in pediatric patients (already negatively affected by the underlying illness) can be significant. In our study, azathioprine was administered to 10 of 11 patients. One patient could not receive azathioprine because of pancytopenia and hair loss induced by azathioprine. Mesalazine was administered to 10 of 11 patients. One patient could not tolerate mesalazine because of pancytopenia. Thus, there is a need for an efficacious treatment for pediatric patients with UC.

The indications for IFX infusion for UC were cases of moderate to severe UC where patients did not respond to treatment with other drugs such as corticosteroid, 6-MP or azathioprine, and where contraindications to these drugs were revealed. In pediatrics, patients with PUCAI scores over 45 are permitted to receive IFX treatment by the Ministry of Health and Welfare. At the period after the third infusion of IFX as an induction regimen, PUCAI scores have to fall by more 20 points compared to the initial treatment period to maintain IFX infusions. For the treatment of moderately to severely active UC, the recommended dose of Remicade (IFX; Schering-Plough Corporation, Kenilworth, NJ, USA) is 5 mg/kg given as an induction regimen at 0, 2, and 6 weeks, followed by a maintenance regimen of 5 mg/kg every 8

weeks thereafter.

Our study showed that 46% of patients were in remission at 8 weeks and 82% of patients were in remission at 54 weeks after IFX treatment. All patients who were steroid-dependent (n=9) before IFX treatment were able to achieve remission and were steroid-free at 54 weeks.

According to previous studies in pediatric UC patients in Western countries, the remission rate after IFX treatment is 38-40%, and the steroid-free rate is 38% at 12 months [13]. In a recent prospective multicenter pediatric study, corticosteroid-free inactive disease in children was observed in 12/44 (27%), 15/39 (38%), and 6/28 (21%) patients at 6, 12, and 24 months after IFX treatment [14]. Our data showed a relatively better response to IFX compared to these studies. However, due to the small study population, there are limitations when it comes to concluding that the response to IFX is more favorable in Korean pediatric UC patients compared to those in Western countries.

All patients who were steroid-refractory (n=2) failed to achieve remission in our study. According to the Outcome of Steroid Therapy in Colitis Individuals study, among corticosteroid-refractory patients receiving IFX, 25 of 33 (75.8%) had a short-term response, and 18 of 33 (54.5%) had a sustained response over 1 year of follow-up [15]. Due to our small study population, the results may have been more unfavorable in steroid-refractory patients in our study.

According to previous studies, the long-term response rate to IFX treatment after 54 weeks was 38-40%. In our study, all short-term responders to IFX were shown to remain in remission, and 80% of the short-term partial responders were able to achieve remission at 54 weeks after IFX treatment. Despite the limitation related to the small study population, it may be that remission at 8 weeks predicts long-term response to IFX and UC remission in pediatric patients.

Thirty-three percent of long-term responders who remained in the state of remission achieved mucosal healing after IFX was stopped. Sixty-seven percent of long-term responders continue to receive IFX as a maintenance treatment, but they are all in remission. Thus, IFX treatment was effective if the patients showed a response in terms of avoiding surgical management.

In summary, this study showed a relatively high response rate to IFX treatment in Korean pediatric UC patients compared to previous Western studies. In addition, neither acute nor delayed adverse events associated with IFX treatment were observed in the other subjects. Moreover, the response to IFX at 8 weeks may predict a favorable long-term response to infliximab treatment in Korean pediatric UC patients. Further large-scale prospective studies are needed in the future.

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