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Infliximab Therapy for Children with Moderate to Severe Ulcerative Colitis: A Step-Up versus a Top-Down Strategy

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Purpose: We aimed to investigate clinical outcomes between top-down (TD) and conventional step-up (SU) therapies in pediatric patients with moderate to severe ulcerative colitis (UC).

Materials and Methods: All patients underwent clinical and endoscopic evaluation at diagnosis and 4 months and 1 year after treatment. Patients who started treatment with corticosteroid were grouped in the SU group, while those that initiated early infliximab (IFX) were grouped in the TD group. Among the SU group, patients who eventually changed to IFX treatment due to steroid resistance or dependency were included in the SU(R) group.

Results: In total, 44 children with moderate to severe UC were included for analysis. Twenty-one patients were included in the SU group, 23 were included in the TD group, and 10 were enrolled in the SU(R) group. Relapse rates were 47.6% (10/21) in the SU group and 17.4% (4/23) in the TD group (p=0.033). Among relapsed patients, the durations from remission to relapse were 17.3 months (0.9–46.9) in the SU group and 24.3 months (1.8–44.9) in the TD group. There was no statistically significant difference in the sustained durations of remission after IFX administration between the SU(R) and TD groups [3.9 (1.4–6.3) and 2.3 (0.3–5.2) years, respectively (p>0.05)].

Conclusion: According to our study, early use of IFX without corticosteroid treatment for children with moderate to severe UC helps to lower relapse rates. We also found that IFX was a very effective treatment for pediatric UC, with a sustained duration of remission similar between TD and SU(R) groups.

Key Words: Ulcerative colitis, infliximab, children

INTRODUCTION

Ulcerative colitis (UC) is an idiopathic bowel disease characterized by repeated improvement and worsening of chronic inflammation of the colonic mucosa and submucosa.[1-3] Abdominal pain, diarrhea, hematochezia, and fecal urgency are common clinical symptoms. Laboratory findings have identified accelerated erythrocyte sedimentation rate, elevated concentrations of C-reactive protein, anemia, and fecal calprotectin as disease activities. The main goal of UC treatment is to achieve and maintain remission of the disease.

Patients with UC require long-term medical involvement due to the difficulty of treatment. More than 20% of UC patients show symptoms before the age of 20 years.[4] UC in children presents a more acute course than adults, and it is not rare for the entire colon to be involved at the time of diagnosis.[5-8] Therefore, pediatric UC may require early treatment augmentation to achieve and maintain disease remission.[9,10]

UC treatment depends on disease activity and endoscopic assessment of inflammatory lesions. Treatment includes the use of 5-aminosalicylic acid compounds, oral or rectal corti-

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costeroids, immunomodulators, and antibiotics, as well as surgical treatment, such as colectomy. Corticosteroids are generally used as a primary treatment in moderate-to-severe UC patients.[9,10] Steroid-treated patients with active UC may show different responses to corticosteroid therapy. Some patients can have good results, achieving symptom-free periods of satisfactory length, while other patients respond well initially, but lose benefits as the treatment is tapered or stopped. Other patients might show complete refractoriness to drugs, despite high doses or prolonged therapies. At a pediatric age, the use of corticosteroids may affect growth or bone density, thus more attention should be directed to their use. In addition, corticosteroid dependencies are more commonly reported in pediatric patients than in adult patients with UC.

The administration of biologics can be introduced in pediatric patients who have not responded to conventional treatments.[7,11,12] Infliximab (IFX), an anti-tumor necrosis factor (TNF)-α monoclonal antibody, has been approved for induction and maintenance treatment and is the first biological therapeutic for pediatric UC.[10] Top-down (TD) therapy may be more beneficial for high-risk pediatric UC patients, such as those with pancolitis or those requiring repetitive corticosteroids; however, studies on a TD strategy are very limited.

Accordingly, we aimed to investigate clinical outcomes between TD and conventional step-up (SU) therapy in pediatric patients with moderate to severe UC.

MATERIALS AND METHODS

Patients and study design

This study was designed as a prospective observational study conducted at the Department of Pediatrics, Samsung Medical Center, between January 2012 and December 2018. The diagnosis of UC was established on the basis of symptoms, laboratory test results, and endoscopic examination according to the Porto criteria.[13] The clinical activity of the disease was evaluated according to Pediatric Ulcerative Colitis Activity Index (PUCAI) score.[14] Mild disease is defined as a PUCAI score of 10–35, moderate disease as a PUCAI score of 40–60, and severe disease as a PUCAI score of 65 or above. Scores of <10 points indicated inactive disease, which was categorized as clinical remission. This study was approved by the Institutional Review Board of Samsung Medical Center and was conducted in accordance with the Declaration of Helsinki (2015-06-003).

Enrolled subjects and their guardians were allowed to choose their initial treatment, either a conventional SU strategy initiated by corticosteroid induction or early IFX administration as a TD strategy without corticosteroid induction, after thorough explanation of the pros and cons of each treatment strategy. The investigator was not involved in the decision-making process on which treatment strategy would be initiated, and written consent was obtained from the subjects and their guardians.

The location and extent of colonic lesions in children during endoscopic examination were assessed based on the Paris classification.[15] According to this classification, ulcerative proctitis (proctitis), left-sided colitis (distal to splenic flexure), extensive colitis (distal to hepatic flexure), and pancolitis (proximal to hepatic flexure) were distinguished.

Twenty-one patients started treatment with corticosteroids, and 23 patients began treatment with the anti-TNF drug IFX [originator, Remicade (Cilag AG, Schaffhausen, Switzerland) and biosimilar, CT-P13 (Celltrion, Incheon, South Korea)]. Treatment in the SU group started with an oral corticosteroid at a dose of 1 mg/kg/day (maximum 60 mg/kg/day) and was tapered over 8 weeks. Almost all of the patients were also administered 5-aminosalicylic acid compounds (mesalazine) and azathioprine. Azathioprine was given at doses of 0.5–1 mg/kg/day and was later modified when required.[16-18] The requirement for dose modification was based on relevant adverse events, laboratory examinations, thiopurine methyltransferase genotype results, and thiopurine metabolite levels of 6-thioguanine nucleotides and 6-methylmercaptopurine. Thiopurine metabolite levels were checked every 1–3 months after 3 months of treatment with azathioprine. Mesalazine was given at a dose of 50 mg/kg/day. Steroid resistance or steroid dependency occurred in 10 of the 21 patients who started treatment with corticosteroids, and they eventually were changed to IFX treatment. IFX was started with no changes in treatment with azathioprine and mesalazine. IFX was administered intravenously at a dose of 5 mg/kg for 0, 2, and 6 weeks. Disease activity was assessed at week 14 after IFX initiation based on the PUCAI, and one patient from the TD group who showed primary non-response to IFX was dropped from the analysis. Scheduled IFX was repeated every 8 weeks from week 14 with clinical response assessments. A reduction in PUCAI score below 10 points indicated clinical remission. Relapse was defined as an increased in PUCAI score by 10 points or more after clinical remission or when new UC treatment needed to be started due to worsening of symptoms.

Baseline demographic data, including sex, birth date, disease classification, growth indicators, and family history of inflammatory bowel disease, were recorded at diagnosis. Physical examination, PUCAI scores, growth indicators, and laboratory examinations, including complete blood cell counts with differential counts, chemistry profiles, erythrocyte sedimentation rate, and C-reactive protein, were assessed before and after treatment. All patients underwent an endoscopic evaluation at diagnosis and at 4 months and 1 year after treatment. The endoscopic appearance of the mucosa was evaluated using the Ulcerative Colitis Endoscopic Index of Severity (UCEIS),[19] which ranged from 0 (normal) to 8 (worst colitis) and has been demonstrated to predict overall endoscopic severity.[19,20]

Outcomes and definition

The primary outcome of this study was the difference in relapse

rates between patients administered an induction therapy with corticosteroids (SU) and those treated with IFX (TD). The secondary outcome was the sustained duration of remission in patients receiving TD treatment compared to patients who relapsed after remission with corticosteroids and subsequently received IFX treatment [SU(R)] (Fig. 1). Adverse events during the study period were also investigated.

Statistical analysis

For comparison of variables between two groups, the two-sample t-test, Mann-Whitney's U-test, chi-square test, and Fisher's exact test were used as appropriate, and the *p* value for statistical significance was defined as $p<0.05$. A ratio difference test was performed to compare the proportion of patients with sustained remission among all patients, including those with ongoing clinical remission. The statistical hypothesis was as follows.

$H_0: P_{TD}=P_{SU}$, $H_1: P_{TD}\neq P_{SU}$

Relapse-free curves were drawn for the cohort using the Kaplan-Meier method with identification of log-rank test. Statistical analysis was carried out using R version 3.6.2 (R Development Core Team, Vienna, Austria).

RESULTS

Baseline characteristics and clinical course

In total, 44 children aged 9–19 years (27 male and 17 female) with moderate to severe UC were included for analysis. Four children were under 10 years, 15 children were 10–15 years old, and the rest were 15–19 years old. Twenty-four patients (54.5%) were diagnosed with pancolitis, 5 patients (11.4%) had extensive lesions in the colon, and the remaining 15 patients (34.1%) had left-sided location of the disease. Among the 44 patients, 21 were included in the SU group, and 23 were included in the TD group. Table 1 shows the demographics and baseline characteristics of the 44 patients. The main symptom of complaint was hematochezia in 36.2%, followed by diarrhea in 27.6%, abdominal pain in 21.9%, and weight loss in 14.3%. Co-administered medications were mesalazine in 40 patients (90.1%), azathioprine in 37 patients (84.1%), and corticosteroids in 21 patients (47.4%).

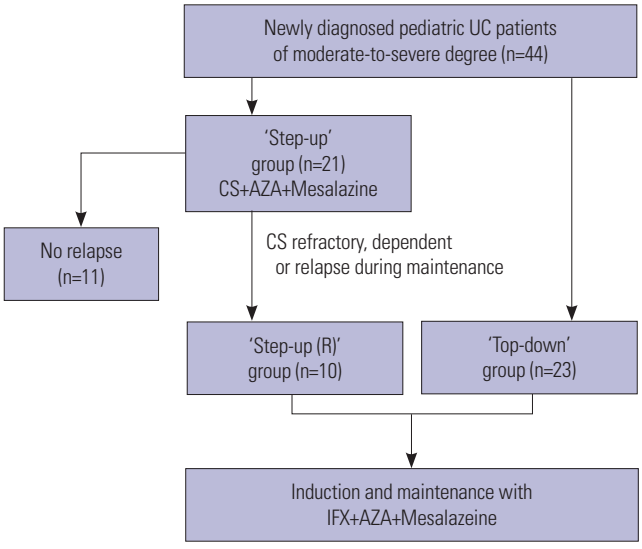

Fig. 1. Schematic outline of patient inclusion and treatment. UC, ulcerative colitis; CS, corticosteroid; IFX, infliximab; AZA, azathioprine.

Comparison of laboratory and endoscopic findings between groups

There were no significant differences in weight, hematocrit, albumin, C-reactive protein, and fecal calprotectin between the SU and TD groups before steroid or IFX treatment. Also, PUCAI scores and UCEIS were not significantly different between the two groups (Table 2). The same items evaluated after 4 months of corticosteroid or IFX treatment also showed no statistical difference between the two groups, except for PUCAI score (Table 3).

Comparison of relapse rates between groups

Relapse rates were 47.6% (10/21) in the SU group and 17.4% (4/23) in the TD group, with a significant difference between the two groups ($p=0.033$). For relapsed patients, the durations from remission to relapse were 17.3 months (0.9–46.9) in the SU group and 24.3 months (1.8–44.9) in the TD group.

Table 1. Baseline Demographics/Clinical Characteristics (n=44)

Sex	
Male	27 (61.4)
Female	17 (38.6)
Age (yr)	15.7 (12.6, 17.4)
Extent of disease	
Left-sided colitis (E2)	15 (34.1)
Extensive colitis (E3)	5 (11.4)
Pancolitis (E4)	24 (54.5)
Symptom	
Abdominal pain	23 (21.9)
Diarrhea	29 (27.6)
Hematochezia	38 (36.2)
Weight loss	15 (14.3)
Duration from diagnosis to CS or IFX, month (IQR)	1.9 (1.3–7.8)
Concomitant medications, at baseline	
Mesalazine	40 (90.1)
Azathioprine	37 (84.1)
Corticosteroids	21 (47.7)

CS, corticosteroid; IFX, infliximab; IQR, interquartile range.
Values represent n (%) or medians (IQR).

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Table 2. Laboratory and Endoscopic Findings between Groups at Baseline

Characteristics	SU (n=21)	TD (n=23)	*p* value
UCEIS	7 (6, 8)	6 (5, 7)	0.348*
PUCAI	50.8 (30, 70)	51.6 (35, 70)	0.843†
CRP (mg/dL)	0.13 (0.03, 2.9)	0.36 (0.12, 1.09)	0.697*
Hematocrit (%)	37.3±5.9	35.8±6.4	0.406†
Albumin (g/dL)	4.1±0.6	4.2±0.5	0.842†
FC (μ/g)	1000 (1000, 1000)	1000 (1000, 1000)	0.688*
Weight (kg)	51 (39, 62.8)	52.9 (44.0, 59.3)	0.636*
Z-scores	-0.5 (-1.6, 0.6)	-0.6 (-1.5, 0.4)	0.598*

TD, top-down; SU, step-up; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; PUCAI, Pediatric Ulcerative Colitis Activity Index; CRP, c-reactive protein; FC, fecal calprotectin; IQR, interquartile range; SD, standard deviation.
Values represent mean±SD or medians (IQR).
*Mann-Whitney's U-test, †t-test.

Table 3. Laboratory and Endoscopic Findings between Groups at 4 Months after Corticosteroid or Infliximab Treatment

Characteristics	SU (n=21)	TD (n=23)	*p* value
UCEIS	3 (1.5, 3)	2.5 (2, 4)	0.565*
PUCAI	10 (5, 20)	5 (0, 5)	0.026†
CRP (mg/dL)	0.06 (0.03, 0.15)	0.05 (0.03, 0.21)	>0.999*
Hematocrit (%)	40.2±5.2	39.4±5.3	0.599†
Albumin (g/dL)	4.5 (4.2, 4.7)	4.5 (4.2, 4.7)	0.841†
FC (μ/g)	1000 (104.7, 1000)	1000 (62.9, 1000)	0.930*
Weight (kg)	51.5 (39, 64.5)	54.2 (42.4, 59.2)	>0.999*
Z-scores	-0.4 (-1.5, 0.7)	-0.5 (-1.3, 0.4)	0.932*

TD, top-down; SU, step-up; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; PUCAI, Pediatric Ulcerative Colitis Activity Index; CRP, c-reactive protein; FC, fecal calprotectin; IQR, interquartile range; SD, standard deviation.
Represent mean±SD or medians (IQR).
*Mann-Whitney's U-test, †t-test.

Comparison of sustained durations of remission between groups after IFX treatment

The SU(R) group, consisting of patients later treated with IFX due to relapse in the SU group, totaled 10 patients. The TD group started IFX 1.3±1.2 months after diagnosis, and the SU(R) group started IFX 19.5±17.1 months after diagnosis. When the sustained duration of remission after IFX administration was compared between the SU(R) and TD groups, there was no statistically significant difference [3.9 (1.4–6.3) and 2.3 (0.3–5.2) years, respectively (p>0.05)]. A ratio difference test was performed to compare the proportion of patients with sustained remission among all patients, including those with ongoing clinical remission. Patients with sustained remission comprised 40% of the SU(R) group and 74% of the TD group, with no significant difference between the groups (p>0.05, 95% CI: -8.5%, 68.2%) (Fig. 2). To evaluate relapse-free curves between the SU(R) and TD groups, Kaplan-Meier survival curves were calculated (Fig. 3). There was no difference in survival rates between two groups (p>0.05). In the evaluation at 1 year after IFX treatment, there were no significant differences between the SU(R) and TD groups for UCEIS, PUCAI, and fecal calprotectin (Table 4).

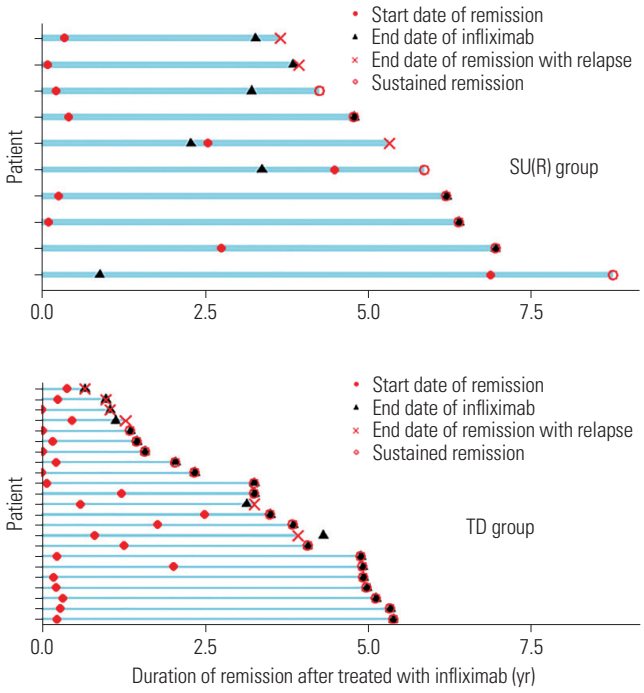

Fig. 2. Comparison of sustained duration of remission between groups after infliximab treatment. A ratio difference test was performed to compare the proportion of patients with sustained remission among all patients, including those with ongoing clinical remission. Patients with sustained remission accounted for 40% of the SU(R) group and 74% of the TD group. There was no significant difference (p>0.05, 95% CI: -8.5%, 68.2%) between groups. SU(R), step-up (relapse); TD, top-down; CI, confidence interval.

Adverse events

There were no major adverse events that led to cessation of corticosteroid or IFX. Other adverse events that occurred during the study period were hair loss (n=6), gastrointestinal disturbance (n=4), skin rash (n=3), and elevation of liver enzymes (n=1). No significant difference in the occurrence of adverse events was observed between groups (p>0.05). During the study period, none of the patients underwent surgical procedures that were related to UC.

DISCUSSION

This is the first study to compare the efficacy of IFX in children and adolescents diagnosed with moderate-to-severe UC who were treated by SU or TD strategies. There is still a lack of concrete and effective treatment for pediatric UC. Currently, medications for UC focus primarily on maintaining symptom control and remission. The natural course of pediatric UC is characterized by greater severity and extensive inflammatory lesions of the colonic mucosa, compared to adults. According to previous studies, UC occurs in children and adolescents in 25% of cases.[8] When it develops in childhood, it is characterized by a

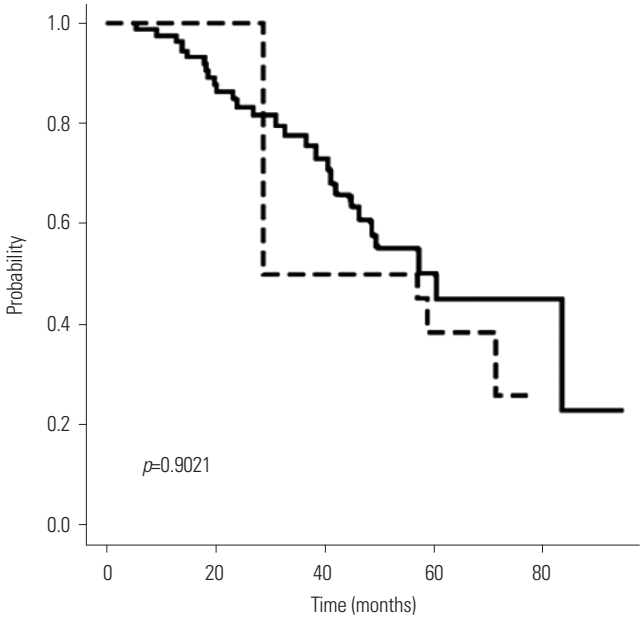

Fig. 3. Relapse-free curves between groups after infliximab treatment. The solid line represents the proportion of the TD group and the dotted line represents the comparable proportion of the SU(R) group. SU(R), step-up (relapse); TD, top-down.

Table 4. Laboratory and Endoscopic Findings between Groups 1 Year after Infliximab Treatment

Characteristics	SU(R) (n = 10)	TD (n = 23)	*p* value
Age at diagnosis, yr (IQR)	14.4 (12.2–17.1)	15.8 (13.1–16.5)	0.574*
Disease extent of Paris classification			0.018*
Left-sided colitis (E2)	2 (20.0)	5 (21.7)	
Extensive colitis (E3)	3 (30.0)	6 (26.1)	
Pancolitis (E4)	5 (50.0)	12 (52.2)	
UCEIS	3 (1, 5)	3 (1.5, 3)	0.489*
PUCAI	0 (0, 5)	0 (0, 10)	0.911†
CRP (mg/dL)	0.08 (0.03, 0.18)	0.06 (0.03, 0.15)	0.961*
Hematocrit (%)	40.5±3.6	41.7±4.2	0.574†
Albumin (g/dL)	4.5 (4.3, 4.6)	4.4 (4.4, 4.6)	0.803†
FC (μ/g)	153.3 (88.5, 218.2)	846.6 (123.3, 1000)	0.272*
Weight (kg)	55.3±14.8	52.7±11.9	0.525*
Z-scores	-0.3±1.3	-0.4±1.1	0.657*

TD, top-down; SU, step-up; UCEIS, Ulcerative Colitis Endoscopic Index of Severity; PUCAI, Pediatric Ulcerative Colitis Activity Index; CRP, c-reactive protein; FC, fecal calprotectin; IQR, interquartile range; SD, standard deviation. Represent mean±SD or medians (IQR).
*Mann-Whitney's U-test, †t-test.

more severe clinical course and numerous acute relapses. Hyams, et al.[21] reported that 57% of 171 children newly diagnosed with UC had moderate to severe disease, and van Limbergen, et al.[6] found that 82% of children had extensive inflammatory changes, compared to 48% of adults. For these reasons, UC in children and adolescents requires more active treatment.

UC treatment in children depends on the disease activity and degree of relapse. Traditionally, 5-aminosalicylic acid preparations, immunomodulators, corticosteroids, and antibiotics are used in the treatment of pediatric patients with moderate to severe UC, and in cases with no improvement, colectomy is recommended.[7,12] While corticosteroids are the most preferred treatment for moderate to severe UC patients, corticosteroid dependence is higher in pediatric patients than in adult patients, and corticosteroid reduction and withdrawal are more important factors for children due to their effects on growth and bone density.[9,10,22] The pathophysiology of glucocorticoid resistance in UC is poorly understood. Some studies suggests that glucocorticoid resistance is associated with T-lymphocytes and possibly other target inflammatory cells.[23] The possible mechanisms of glucocorticoid resistance in UC might be decreased cytoplasmic glucocorticoid concentrations, secondary to increased P-glycoprotein-mediated efflux of glucocorticoid from target cells due to overexpression of the multidrug resistance gene *MDR1*. Other potential mechanisms include impaired glucocorticoid signaling because of dysfunction at the level of the glucocorticoid receptor and constitutive epithelial activation of proinflammatory mediators, including nuclear factor kappa B, resulting in inhibition of glucocorticoid receptor transcriptional activity.[24]

IFX, is the first biological preparation officially approved for the treatment of moderate to severe UC in adults and children. IFX is a human-mouse chimeric IgG monoclonal antibody that specifically binds to TNF-α to prevent the interaction of TNF-α with cellular receptors, thereby reducing inflammation and damage caused by the overproduction of TNF-α.[25] Since IFX was introduced in UC treatment, several studies have shown that it is effective in the induction and maintenance of clinical remission. IFX has also contributed to reduction in the use of steroids and colectomy.[7,14,26-28] Hyams, et al.[29] identified the efficacy of IFX in the treatment of pediatric patients with moderate to severe UC. After induction treatment, a clinical response was induced in 73.3% of patients, and 28.6% of patients were in clinical remission within the 54th week.

Even though there have been several studies on the effectiveness of IFX in UC therapy, no studies have focused on TD therapy because UC responds better to 5-aminosalicylic acid drugs or corticosteroids than Crohn's disease.[30,31] However, about 30–40% of UC patients have pancolitis, and this rate is higher in pediatric patients.[32,33] Patients with pancolitis eventually require colectomy in about 50% of cases within 5 years of diagnosis. In addition, about one-third of patients in need of steroid therapy will finally require colectomy.[30] In children with UC, there are many factors that can predict a poorer prognosis than adults, thus it seems that active TD therapy is necessary.

According to our study, early use of IFX in children with moderate to severe UC helps lower relapse rates. Approximately 50% of patients who started treatment with corticosteroids eventually experienced relapse. In the SU group, corticosteroid achieved disease remission, but it could not continue to be used as a maintenance therapy. Therefore, it is not unexpected that its

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relapse rate was higher than that in the TD group wherein IFX use continued as a maintenance therapy. A novel result of our study is that 'step-up' with IFX in patients who relapsed after using corticosteroids was as effective as TD therapy: the sustained duration of remission in the SU(R) group did not differ significantly from that of the TD group even after IFX was initiated at relapse.

The limitations of this study are its small sample size and selection bias due to the lower prevalence of UC in children than in adults and this being a single institutional study. The total number of subjects is not large enough, and the number of SU(R) individuals was even smaller. This might be a drawback of the study. Therefore, further large-scale multicenter studies are required in the future to confirm our findings. Selection bias may also have been introduced by entrusting treatment choices to subjects and their guardians. Given that subjects and guardians chose the initial treatment, a lack of blinding and inappropriate randomization are major issues that may limit the significance of the study, which is a limitation of prospective observational studies such as ours, where decisions are made while the investigators and subjects are aware of the study hypothesis.

In conclusion, TD therapy with IFX without corticosteroid use was effective in pediatric patients with moderate to severe UC. Additionally, we found that IFX was effective in maintenance treatment for UC since the sustained duration of remission in the SU(R) group did not differ significantly from the TD group even after IFX was used later at relapse. According to our results, we recommend that IFX administration be provided early to children with moderate to severe UC.

AUTHOR CONTRIBUTIONS

Conceptualization: Mi Jin Kim and Yon Ho Choe. Data curation: Eunsil Kim and Ben Kang. Formal analysis: all authors. Investigation: Mi Jin Kim and Eunsil Kim. Methodology: Ben Kang and Yon Ho Choe. Project administration: Mi Jin Kim and Ben Kang. Resources: Mi Jin Kim and Yon Ho Choe. Software: Mi Jin Kim and Ben Kang. Supervision: Ben Kang and Yon Ho Choe. Validation: Mi Jin Kim and Yon Ho Choe. Visualization: Mi Jin Kim and Yon Ho Choe. Writing—original draft: Mi Jin Kim. Writing—review & editing: Ben Kang and Yon Ho Choe. Approval of final manuscript: all authors.

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REFERENCES

1. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 2010;105:501-23.
2. Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet 2012;380:1606-19.
3. Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, et al. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011;60:571-607.
4. Baldassano RN, Piccoli DA. Inflammatory bowel disease in pediatric and adolescent patients. Gastroenterol Clin North Am 1999;28:445-58.
5. Dotson JL, Hyams JS, Markowitz J, LeLeiko NS, Mack DR, Evans JS, et al. Extraintestinal manifestations of pediatric inflammatory bowel disease and their relation to disease type and severity. J Pediatr Gastroenterol Nutr 2010;51:140-5.
6. Van Limbergen J, Russell RK, Drummond HE, Aldhous MC, Round NK, Nimmo ER, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology 2008;135:1114-22.
7. Sylvester FA, Turner D, Draghi A 2nd, Uuosoe K, McLernon R, Koproske K, et al. Fecal osteoprotegerin may guide the introduction of second-line therapy in hospitalized children with ulcerative colitis. Inflamm Bowel Dis 2011;17:1726-30.
8. Griffiths AM. Specificities of inflammatory bowel disease in childhood. Best Pract Res Clin Gastroenterol 2004;18:509-23.
9. Ruemmele FM, Turner D. Differences in the management of pediatric and adult onset ulcerative colitis--lessons from the joint ECCO and ESPGHAN consensus guidelines for the management of pediatric ulcerative colitis. J Crohns Colitis 2014;8:1-4.
10. Turner D, Levine A, Escher JC, Griffiths AM, Russell RK, Dignass A, et al. Management of pediatric ulcerative colitis: joint ECCO and ESPGHAN evidence-based consensus guidelines. J Pediatr Gastroenterol Nutr 2012;55:340-61.
11. Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol 2011;106:644-59.
12. Turner D, Walsh CM, Benchimol EI, Mann EH, Thomas KE, Chow C, et al. Severe paediatric ulcerative colitis: incidence, outcomes and optimal timing for second-line therapy. Gut 2008;57:331-8.
13. IBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. Inflammatory bowel disease in children and adolescents: recommendations for diagnosis--the Porto criteria. J Pediatr Gastroenterol Nutr 2005;41:1-7.
14. Turner D, Walsh CM, Steinhart AH, Griffiths AM. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. Clin Gastroenterol Hepatol 2007;5:103-10.
15. Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis 2011;17:1314-21.
16. Amin J, Huang B, Yoon J, Shih DQ. Update 2014: advances to optimize 6-mercaptopurine and azathioprine to reduce toxicity and improve efficacy in the management of IBD. Inflamm Bowel Dis 2015;21:445-52.
17. Lee MN, Kang B, Choi SY, Kim MJ, Woo SY, Kim JW, et al. Relationship between azathioprine dosage, 6-thioguanine nucleotide levels, and therapeutic response in pediatric patients with IBD treated with azathioprine. Inflamm Bowel Dis 2015;21:1054-62.
18. Kim MJ, Choe YH. Monitoring and safety of azathioprine therapy in inflammatory bowel disease. Pediatr Gastroenterol Hepatol Nutr 2013;16:65-70.
19. Travis SP, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, et al. Developing an instrument to assess the endoscopic severity of ulcerative colitis: the Ulcerative Colitis Endoscopic Index

of Severity (UCEIS). Gut 2012;61:535-42.
20. Travis SP, Schnell D, Krzeski P, Abreu MT, Altman DG, Colombel JF, et al. Reliability and initial validation of the ulcerative colitis endoscopic index of severity. Gastroenterology 2013;145:987-95.
21. Hyams JS, Davis P, Grancher K, Lerer T, Justinich CJ, Markowitz J. Clinical outcome of ulcerative colitis in children. J Pediatr 1996;129:81-8.
22. Jakobsen C, Bartek J Jr, Wewer V, Vind I, Munkholm P, Groen R, et al. Differences in phenotype and disease course in adult and paediatric inflammatory bowel disease--a population-based study. Aliment Pharmacol Ther 2011;34:1217-24.
23. McManus R. Mechanisms of steroid action and resistance in inflammation and disease. J Endocrinol 2003;178:1-4.
24. Bianchi Porro G, Cassinotti A, Ferrara E, Maconi G, Ardizzone S. Review article: the management of steroid dependency in ulcerative colitis. Aliment Pharmacol Ther 2007;26:779-94.
25. Danese S. Mechanisms of action of infliximab in inflammatory bowel disease: an anti-inflammatory multitasker. Dig Liver Dis 2008;40 Suppl 2:S225-8.
26. Rutgeerts P, Sandborn WJ, Feagan BG, Reinisch W, Olson A, Johanns J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462-76.
27. Järnerot G, Hertervig E, Friis-Liby I, Blomquist L, Karlén P, Grännö C, et al. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. Gastroenterology 2005;128:1805-11.
28. Turner D, Mack D, Leleiko N, Walters TD, Uusoue K, Leach ST, et al. Severe pediatric ulcerative colitis: a prospective multicenter study of outcomes and predictors of response. Gastroenterology 2010;138:2282-91.
29. Hyams J, Damaraju L, Blank M, Johanns J, Guzzo C, Winter HS, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol 2012;10:391-9.e1.
30. Sandborn WJ. What's new: innovative concepts in inflammatory bowel disease. Colorectal Dis 2006;8 Suppl 1:3-9.
31. Matula S, Croog V, Itzkowitz S, Harpaz N, Bodian C, Hossain S, et al. Chemoprevention of colorectal neoplasia in ulcerative colitis: the effect of 6-mercaptopurine. Clin Gastroenterol Hepatol 2005;3:1015-21.
32. Tajiri H, Arai K, Kagimoto S, Kunisaki R, Hida N, Sato N, et al. Infliximab for pediatric patients with ulcerative colitis: a phase 3, open-label, uncontrolled, multicenter trial in Japan. BMC Pediatr 2019;19:351.
33. Adedokun OJ, Xu Z, Padgett L, Blank M, Johanns J, Griffiths A, et al. Pharmacokinetics of infliximab in children with moderate-to-severe ulcerative colitis: results from a randomized, multicenter, open-label, phase 3 study. Inflamm Bowel Dis 2013;19:2753-62.

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