ABSTRACT

Purpose: The long-term efficacy and safety of infliximab (IFX) in children with ulcerative colitis (UC) have not been well-evaluated. Here, we reviewed the long-term durability and safety of IFX in our single center pediatric cohort with UC.

Methods: This retrospective study included 20 children with UC who were administered IFX.

Results: For induction, 5 mg/kg IFX was administered at weeks 0, 2, and 6, followed by every 8 weeks for maintenance. The dose and interval of IFX were adjusted depending on clinical decisions. Corticosteroid (CS)-free remission without dose escalation (DE) occurred in 30% and 25% of patients at weeks 30 and 54, respectively. Patients who achieved CS-free remission without DE at week 30 sustained long-term IFX treatment without colectomy. However, one-third of the patients discontinued IFX treatment because of a primary nonresponse, and one-third experienced secondary loss of response (sLOR). IFX durability was higher in patients administered IFX plus azathioprine for >6 months. Four of five patients with very early onset UC had a primary nonresponse. Infusion reactions (IRs) occurred in 10 patients, resulting in discontinuation of IFX in four of these patients. No severe opportunistic infections occurred, except in one patient who developed acute focal bacterial nephritis. Three patients developed psoriasis-like lesions.

Conclusion: IFX is relatively safe and effective for children with UC. Clinical remission at week 30 was associated with long-term durability of colectomy-free IFX treatment. However, approximately two-thirds of the patients were unable to continue IFX therapy because of primary nonresponse, sLOR, IRs, and other side effects.

Keywords: Dose escalation; Infliximab; Child; Remission; Ulcerative colitis

INTRODUCTION

Pediatric-onset ulcerative colitis (UC) accounts for 15–20% of all UC cases [1]. Compared with adult-onset UC, pediatric patients tend to have more extensive and severe disease. Van
Limbergen et al. [2] reported that approximately 75% of children with UC had pancolitis at diagnosis as opposed to 48% of adults with UC and that 46% of children without pancolitis at diagnosis eventually developed the condition. Children with UC are at high risks of developing severe colitis, failing to respond to corticosteroid (CS) therapy, and requiring biologics [2,3].

Infliximab (IFX) is a chimeric immunoglobulin G-1 monoclonal antibody to tumor necrosis factor alpha (TNF-α). In the United States, Canada, the European Union, and Japan, IFX has been approved for children aged ≥6 years with moderate-to-severe UC refractory to conventional treatment. As a short-term outcome, Hyams et al. [4] reported a remission rate of 28.6% at week 54 in children with UC that was refractory to conventional treatment. However, a substantial proportion of children with UC or Crohn’s disease (CD) who initially responded to IFX induction therapy eventually became treatment-resistant [3,5]. Studies describing the long-term efficacy and durability of IFX in children with UC for >1 year are limited.

In this study, we retrospectively reviewed the long-term durability and safety of IFX therapy in pediatric patients with UC who were followed in a single tertiary care pediatric inflammatory bowel disease (IBD) center in Japan for up to 9 years.

**MATERIALS AND METHODS**

**Study design, subjects, and ethical approval**

This retrospective study was conducted at the National Center for Child Health and Development (NCCHD), Tokyo, Japan. Pediatric patients aged <17 years who were newly administered IFX to treat UC from April 2008 to March 2018 and followed for ≥1 year were included in the study. Patients who were introduced to IFX in other institutions or who were not followed up at our institution for more than 1 year were excluded from this study. UC diagnosis was based on the diagnostic criteria developed by the Paediatric IBD Porto Group of ESPGHAN [6]. This study was approved by the institutional ethics review board of the NCCHD (No. 1550).

**Data collection**

The patients’ medical records were reviewed retrospectively, and data describing the following characteristics were analyzed: demographic data, extent and severity of disease at baseline according to the Paris classification [7], pediatric ulcerative colitis activity index (PUCAI), previous and concomitant use of medications, and IFX therapy including the dosage and adverse events (AEs) experienced.

Clinical remission was defined as a PUCAI of <10 points without an increase in CS [8]. A primary nonresponse (PNR) was defined as a failure to respond to IFX therapy by week 30; patients whose PUCAI did not improve and/or who required a CS dose increase to control their symptoms were considered as having failed to respond. However, in patients who used a CS at the initiation of IFX, if the patient’s PUCAI was less than 30 points and the CS dose was reduced to <50% of the original dose within 30 weeks, the case was not regarded as a PNR, even if the PUCAI increased. A secondary loss of response (sLOR) was defined as the loss of response after an initial response. The reasons for discontinuing IFX were categorized as PNR, sLOR, infusion reactions (IRs), or another treatment-limiting AE. Dose escalation (DE) of IFX maintenance therapy was defined as either a dose increase of ≥7.5 mg/kg or a shorter interval of <6 weeks [3].
Statistical analyses

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Student’s t-test was used to compare differences in continuous variables between groups. Fisher’s exact analysis was used to determine whether two categorical variables were associated with each other. Kaplan–Meier curve with log-rank test was used to analyze the IFX durability. Results showing a p-value of <0.05 were considered as statistically significant.

RESULTS

Patient demographics

A cohort of 20 patients who were newly administered IFX and followed up for >1 year was included in this analysis. Table 1 shows the patients’ demographic data. Five patients were diagnosed at <6 years of age and categorized as very early onset (VEO)-UC. In three of these patients, whole exome sequencing (WES) was conducted and no known monogenic IBD was identified. The other two patients were transferred to other hospitals, and WES was not performed. Sixteen (80%) patients used CS at the first IFX infusion. Azathioprine (AZA) was administered concomitantly to 14 (70%) patients at the first IFX infusion; of these patients, nine continued using AZA and IFX for >6 months and five discontinued AZA within 6 months (Table 2).

Short-term outcome at week 30

Fig. 1 presents a flow diagram of the patients. At week 30, six (30%) patients achieved CS-free clinical remission without DEs. PNR occurred in eight patients (Table 2), and these patients

Table 1. Patients’ demographics

| No. | Sex | Age at diagnosis (yr) | Very early onset UC | Paris classification | Age at the first IFX (yr) | Body weight (kg) | Concomitant medications at first IFX | Extraintestinal manifestations |
|-----|-----|----------------------|---------------------|----------------------|--------------------------|-----------------|-------------------------------------|-------------------------------|
| 1   | F   | 12                   | −                   | A1b E4 S0           | 14                       | 48              | + + −                               | −                             |
| 2   | F   | 15                   | −                   | A1b E4 S1           | 16                       | 48              | + + +                               | −                             |
| 3   | M   | 11                   | −                   | A1b E4 S0           | 12                       | 32              | x + +                               | −                             |
| 4   | F   | 10                   | −                   | A1b E4 S1           | 13                       | 40              | + + x                               | x                             |
| 5   | F   | 16                   | −                   | A1b E4 S1           | 16                       | 46              | x − +                               | 40 mg                         |
| 6   | F   | 9                    | −                   | A1a E4 S0           | 11                       | 34              | + + −                               | 2.5 mg                        |
| 7   | F   | 8                    | −                   | A1a E4 S1           | 10                       | 37              | − − +                               | 20 mg                         |
| 8   | F   | 11                   | −                   | A1b E4 S1           | 12                       | 38              | x + +                               | −                             |
| 9   | F   | 11                   | −                   | A1b E4 S1           | 15                       | 56              | + + x                               | 10 mg                         |
| 10  | M   | 12                   | −                   | A1b E4 S0           | 14                       | 45              | x + −                               | −                             |
| 11  | F   | 4                    | +                   | A1a E4 S1           | 5                        | 17              | x − −                               | 7.5 mg PSC                    |
| 12  | M   | 12                   | −                   | A1b E4 S1           | 12                       | 33              | x − −                               | 20 mg                         |
| 13  | M   | 15                   | −                   | A1b E4 S1           | 17                       | 58              | + + −                               | −                             |
| 14  | F   | 11                   | −                   | A1b E4 S1           | 11                       | 29              | x − −                               | 30 mg                         |
| 15  | M   | 5                    | +                   | A1a E3 S1           | 6                        | 16              | + + +                               | 15 mg                         |
| 16  | F   | 1                    | +                   | A1a E4 S1           | 1                        | 9               | x + +                               | 6 mg                          |
| 17  | M   | 2                    | +                   | A1a E4 S1           | 2                        | 10              | x + +                               | 4 mg                          |
| 18  | F   | 2                    | +                   | A1a E4 S1           | 2                        | 13              | x + +                               | 20 mg                         |
| 19  | F   | 8                    | −                   | A1a E4 S0           | 10                       | 24              | x − −                               | x                             |
| 20  | F   | 11                   | −                   | A1b E4 S0           | 12                       | 35              | + + −                               | 20 mg                         |

UC: ulcerative colitis, IFX: infliximab, AZA: azathioprine, TAC: tacrolimus, CS: corticosteroid, F: female, M: male, +: ongoing use, x: previously used, −: never used, PSC: primary sclerosing cholangitis.

According to the Paris classification, for age at diagnosis: A1a, 0–<10 years; A1b, 10–<17 years; for extent: E3, Extensive (hepatic flexure distally); E4, Pancolitis (proximal to hepatic flexure); and for severity: S0, never severe; S1, at least once severe. Severe defined by Pediatric Ulcerative Colitis Activity index ≥65.
Table 2. Clinical Characteristics of the Patients

| No. | Sex | Age | Duration of concomitant use with IFX | Week 30 evaluation | sLOR Onset (wk) | DE Onset (wk) | Adverse event Onset (wk) | At the last follow-up |
|-----|-----|-----|--------------------------------------|--------------------|----------------|---------------|------------------------|----------------------|
|     |     |     | At diagnosis (yr) | At the first IFX (yr) | AZA (wk) | TAC (wk) | CS (wk) | Clinical remission | PNR | Status of IFX maintenance therapy | Duration of IFX therapy (wk) | Reason for discontinuation | Final outcome |
| 1   | F   | 12  | 14                      | 54                  | 22      | +       | -       | -                    | -       | AFBN                          | 95                             | Continuing                     | Transferred |
| 2   | F   | 15  | 16                      | 204                 | 1       | 14      | +       | -                    | -       | Continuing                    | 250                            | -                             | Transferred |
| 3   | M   | 11  | 12                      | 30                  | 0       | 2       | -       | -                    | -       | Acne vulgaris                 | 44                             | Ceased                        | Switched to GLM |
| 4   | F   | 10  | 13                      | 316                 | -       | -       | +       | -                    | +       | 38                             | 82                            | Continuing                     | Transferred |
| 5   | F   | 16  | 16                      | -                   | 5       | 17      | +       | -                    | +       | 142                           | -                             | IR (urticaria)                | 240                             | Ceased                        | Switched to GLM |
| 6   | F   | 9   | 11                      | 45                  | -       | 2       | -       | -                    | +       | 112                           | +                             | 165                           | -                             | Ceased                        | sLOR Colectomy |
| 7   | F   | 8   | 10                      | 273                 | 1       | 95      | +       | -                    | +       | 96                             | -                             | IR (urticaria)                | 142                           | Ceased                        | Switch to GLM |
| 8   | F   | 12  | 13                      | 13                  | 3       | 13      | -       | +                    | -       | -                             | -                             | -                             | Ceased                        | 13 PNR Colectomy |
| 9   | F   | 11  | 15                      | 211                 | -       | 53      | -       | -                    | +       | 14                            | +                             | 36                            | IR (flushing)                 | 211                           | -                             | Transferred |
| 10  | M   | 12  | 14                      | 123                 | -       | 69*     | -       | -                    | -       | +                             | 54                            | 60                            | -                             | Ceased                        | sLOR Colectomy |
| 11  | F   | 4   | 5                       | -                   | 241     | -       | -       | +                    | 20      | +                             | 27                            | IR (urticaria)                | 142                           | Ceased                        | Switched to IFX |
| 12  | M   | 12  | 12                      | 31                  | -       | 14      | +       | -                    | +       | 138                           | +                             | 138                           | -                             | Ceased                        | sLOR Colectomy |
| 13  | M   | 15  | 17                      | 12                  | -       | -       | -       | -                    | -       | -                             | -                             | -                             | -                             | Ceased                        | 12 PNR Switched to CM |
| 14  | F   | 11  | 11                      | -                   | 1       | -       | +       | -                    | -       | -                             | -                             | -                             | -                             | Ceased                        | 1 PNR Colectomy |
| 15  | M   | 5   | 6                       | 4                   | 17      | 17      | +       | -                    | -       | -                             | -                             | IR (tachycardia)              | 9                             | Ceased                        | 17 PNR CM                  |
| 16  | F   | 1   | 1                       | 49                  | 19      | 49      | +       | -                    | +       | -                             | +                             | 23                            | IR (tachycardia, vomiting)   | 4                             | Ceased                        | 49 PNR Colectomy |
| 17  | M   | 2   | 2                       | 7                   | 7       | 7       | -       | +                    | -       | -                             | -                             | IR (tachycardia, skin rash)   | 3                             | Ceased                        | 7 PNR, IR Switched to CS    |
| 18  | F   | 2   | 2                       | 1                   | 9       | 9       | -       | +                    | -       | -                             | -                             | IR (flushing)                 | 5                             | Ceased                        | 9 PNR Colectomy |
| 19  | F   | 8   | 10                      | -                   | -       | -       | +       | -                    | +       | 12                            | -                             | PLSL                          | 5                             | IR (dyspnea)                  | 29                            | Ceased                        | 29 PNR, IR Switched to GLM |
| 20  | F   | 11  | 12                      | 45                  | -       | 19      | -       | +                    | 34      | +                             | 11                            | IR (urticaria)                | 40                            | Ceased                        | 45 sLOR, IR Switched to GLM |

IFX: infliximab, AZA: azathioprine, TAC: tacrolimus, CS: corticosteroid, PNR: primary non-response, sLOR: secondary loss of response, DE: dose escalation, AE: adverse event, F: female, M: male, -: never used, +: ongoing use, AFBN: acute focal bacterial nephritis, Transferred: transferred from our children's hospital to other hospitals because their age reached to adult age, IR: infusion reaction, PLSL: psoriasis-like skin lesion, GLM: golimumab, CM: Chinese medicine.

*Corticosteroid was reintroduced at week 55.
tended to be diagnosed and treated with IFX at a younger age than the others (Table 3). Of these, seven ceased IFX treatment by week 30, including three who underwent colectomy, two who switched to non-approved Chinese medicine, one who switched to golimumab (GLM), and one who required CS (Table 2). Long-term remission was not maintained in any patients who showed PNR.

**Long-term durability assessment**

As shown in Fig. 1, the CS-free and DE-free clinical remission at week 54 occurred in 25.0% of cases (5/20). After excluding eight patients who had PNR by week 30, CS-free and DE-free clinical remission occurred in 41.7% (5/12). Fig. 2A shows the Kaplan–Meier curve of the overall colectomy-free survival.

**Fig. 1.** Patient flow chart.

DE: dose escalation, IFX: infliximab, CS: corticosteroid, PNR: primary nonresponse, sLOR: secondary loss of response, GLM: golimumab, AE: adverse event.
Table 3. Comparison of clinical characteristics between primary non-responders and the others

|                         | PNR (n=8) | Non PNR (n=12) | p-value |
|-------------------------|-----------|----------------|---------|
| Female                  | 5 (62.5)  | 9 (75.0)       | 0.64    |
| Age (yr)                |           |                |         |
| At onset                | 6.8±5.3   | 10.7±3.3       | 0.06    |
| At diagnosis            | 6.9±5.1   | 10.9±3.1       | 0.04    |
| At first IFX            | 7.6±5.8   | 12.5±3.0       | 0.02    |
| Duration between        |           |                |         |
| Diagnosis and first IFX (wk) | 42±45 | 86±73           | 0.15    |
| Paris classification    |           |                |         |
| Extent E4               | 7 (87.5)  | 12 (100.0)     | 0.40    |
| Severity S1             | 7 (87.5)  | 7 (58.3)       | 0.33    |
| Concomitant medications |           |                |         |
| 5-ASA                   | 2 (25.0)  | 7 (58.3)       | 0.20    |
| AZA                     | 6 (75.0)  | 8 (66.7)       | 1.00    |
| TAC                     | 5 (62.5)  | 4 (33.3)       | 0.36    |
| CS                      | 6 (75.0)  | 10 (83.3)      | 1.00    |

Values are presented as number (%) or mean±standard deviation.
PNR: primary non-responder, IFX: infliximab, 5-ASA: 5-aminosalicylic acid, AZA: azathioprine, TAC: tacrolimus, CS: corticosteroid.

Fig. 2. Kaplan–Meier survival curves of pediatric patients with ulcerative colitis administered infliximab. (A) Overall colectomy-free survival. (B) Comparison of colectomy-free survival with and without remission at week 30. (C) sLOR-free IFX continuation rate. Primary non-responders were excluded. (D) Comparison of sLOR-free IFX continuation rate with and without >6 months of azathioprine combination therapy. Primary non-responders were excluded. sLOR: secondary loss of response, IFX: infliximab.
Six (30%) patients underwent colectomy during the study period. Their median IFX treatment duration was 31 weeks (range: 1–240 weeks). Four of these patients had PNR and two experienced sLOR.

Fig. 2B shows the Kaplan–Meier curves for colectomy-free survival in patients who were and were not in remission at week 30. All seven patients in clinical remission at week 30 avoided colectomy during the study period, and two achieved long-term CS-free and DE-free sustained clinical remission for more than 7 years. In contrast, seven of the 13 patients who did not achieve clinical remission at week 30 continued IFX after week 30, three patients underwent colectomy, one remained dependent on CS, two switched to GLM, and one achieved CS-free remission with DE (Table 2).

Fig. 2C presents the Kaplan–Meier curve for sLOR-free IFX continuation. Within this group of 12 patients, which excluded eight patients who had PNR, 9 (75.0%) experienced sLOR during follow-up.

Outcomes in patients with very early-onset ulcerative colitis
Of the five patients with VEO-UC, one patient with primary sclerosing cholangitis maintained remission on a low dose of CS and continued IFX for >4 years. The remaining four patients had PNR and ceased IFX. DE was not effective in these patients, and they remained CS-dependent. Overall, no patients with VEO-UC achieved CS-free remission with IFX treatment.

Monotherapy versus combination therapy
The durability of IFX therapy was compared between patients who continued AZA combination therapy for >6 months and those who continued AZA combination therapy ≤6 months or IFX monotherapy (Fig. 2D). There was no significant difference in the background of the two groups (Table 4). Administration of combination therapy for >6 months was not associated with a significantly higher sLOR free IFX continuation rate compared with combination therapy administered for <6 months or IFX administered alone (p=0.53). However, three patients who continued IFX therapy for more than 3 years without experiencing sLOR continued combination therapy >6 months.

Table 4. Clinical characteristics compared by with and without the concomitant use of AZA for more than 6 months

|                        | AZA ≤6 mo (n=9) | AZA >6 mo (n=11) | p-value |
|------------------------|----------------|-----------------|---------|
| Female                 |                |                 | 1.00    |
| Age (yr)               |                |                 |         |
| At onset               | 8.1±5.4        | 9.9±3.8         | 0.40    |
| At diagnosis           | 8.2±5.3        | 10.2±3.5        | 0.34    |
| At first IFX           | 9.0±5.6        | 11.8±4.0        | 0.21    |
| Duration between       |                |                 | 0.07    |
| Diagnosis and first IFX (wk) | 39±43 | 92±73          |         |
| Paris classification    |                |                 |         |
| Extent E4              | 8 (88.9)       | 11 (100.0)      | 0.45    |
| Severity S1            | 8 (88.9)       | 6 (54.5)        | 0.16    |
| Concomitant medications|                |                 |         |
| 5-ASA                  | 2 (22.2)       | 7 (63.6)        | 0.09    |
| AZA                    | 5 (55.6)       | 9 (81.8)        | 0.34    |
| TAC                    | 5 (55.6)       | 4 (36.4)        | 0.65    |
| CS                     | 7 (77.8)       | 9 (81.8)        | 1.00    |

Values are presented as number (%) or mean±standard deviation.
AZA: azathioprine, IFX: infliximab, 5-ASA: 5-aminosalicylic acid, TAC: tacrolimus, CS: corticosteroid.
Corticosteroid-sparing effect

At the first IFX infusion, CS was administered to 16 of 20 patients concomitantly. CS therapy was successfully discontinued in nine of ten patients (90%) who had no PNR; CS therapy was resumed in all six patients who had PNR.

Adverse events

One patient (5%) developed acute focal bacterial nephritis that was successfully treated with intravenous antibiotics, and the patient continued IFX therapy without an acute focal bacterial nephritis recurrence. Except for this patient, no patients developed serious opportunistic infections requiring admission and/or IFX treatment cessation. No malignancies or deaths occurred during the study period.

By week 30, five patients experienced IRs, including tachycardia, vomiting, rashes, and shortness of breath. Although three of these patients used premedication, which comprised hydrocortisone, acetaminophen, and hydroxyzine, and/or reduced their IFX infusion rates to enable them to continue IFX treatment, two patients discontinued IFX because of the IRs. After week 30, five more patients experienced IRs; two of these patients discontinued IFX because of the IRs. Finally, among the 10 patients (50%) who experienced IRs, four switched to GLM, two underwent colectomy, and two switched to other therapies, including CS and non-approved Chinese medicine (Table 1). Only two of 10 patients continued IFX throughout the study period.

Three (15%) patients developed psoriasis-like skin lesions, most frequently involving the face and scalp. Topical treatments, which comprised vitamin D ointment and CS ointment, improved the skin lesions in one patient, and the remaining patients eventually switched to GLM because their psoriasis-like skin lesions were resistant to topical treatments and their intestinal lesions stopped responding to IFX treatment.

DISCUSSION

In this study, we evaluated a cohort of 20 children with UC who were treated with IFX for up to 9 years (median, 143 weeks; interquartile range, 26–256 weeks). The short-term outcome, namely, CS-free clinical remission without DE, was achieved in 30% of patients at week 30, and two-thirds of these patients sustained CS-free remission without DE for >4 years. Notably, two patients sustained very long-term CS-free remission for >7 years. However, the long-term results showed that approximately one-third of the patients had PNR and discontinued IFX and that a further one-third experienced sLOR and required DEs. By the end of the fourth year, 11 patients (55%) had discontinued IFX.

Hyams et al. [3] reported a multicenter cohort study of 52 patients with UC who were administered IFX, and CS-free inactive disease was 38% in the first year. Another IFX study conducted by Hyams et al. [9] in pediatric patients with moderate-to-severe UC demonstrated that the week 54 remission rate in week 8 responders was 38.1%, which agrees with our study results.

In this study, eight patients had PNR, among whom four were VEO-UC. As many as 80% of the VEO-UC patients showed PNR, as previously reported [10]. One patient showed severe IR, and IFX was ceased. He showed no clinical improvement. Another patient did not respond to IFX and depended on CS. In these patients, some pathogenic factors other than...
TNF-α may have contributed to their colitis. Although the other two patients responded well to IFX, they relapsed a few days later; the serum IFX concentration of one of these patients was <0.10 ng/mL, despite having IFX infusion 2 weeks prior. Both patients had low serum albumin levels. Patients with severe diarrhea and/or severe inflammation tended to lose IFX at a much faster rate, as it is excreted in the stool and consumed by neutralizing TNF-α.

In summary, the effect of IFX was limited in patients with VEO-UC, and further studies are needed to determine optimal treatment strategy in these patients. In addition to patients with VEO-UC, four non-VEO patients had PNR. Two were refractory to IFX treatment and underwent colectomy, one started using non-approved Chinese medicine, and one switched to GLM because she experienced IR to IFX. The switch to GLM did not cause an IR, nor was it effective. Patients with PNR should be switched to therapeutics other than anti-TNF-α inhibitors [11].

The decrease in the durability of IFX is a critical issue. A previous study indicated that 20–50% of pediatric patients with CD experienced sLOR within 1 year [5]. In this study, four of the 12 patients without PNR (33%) showed sLOR within 1 year. The number of patients who experienced sLOR continued to increase after the first year. Overall, ten of the 12 patients (83%) eventually experienced sLOR. Although eight of the 10 patients with sLOR went to a higher dose of IFX, only two patients responded to IFX and recovered to achieve sustained clinical remissions. Moreover, six of the ten patients with sLOR experienced IRs, though premedication and/or infusion rate reductions enabled them to continue IFX therapy. Most of these failures are thought to be associated with production of antibodies to IFX (ATI) and low serum IFX levels [5]. Combination therapy with an immunomodulator has been used to prevent ATI production and maintain serum IFX levels based on data from the SONIC trial by Colombel et al. [12], which reported that combination therapy was associated with a higher CS-free clinical remission rate at week 26, higher IFX trough level, and lower incidence of ATI at week 30 compared with monotherapy. However, Lichtenstein et al. [13] evaluated data from four prospective randomized trials and concluded that although combination therapy reduced IRs and immunogenicity, there were no consistent differences in the serum IFX levels between combination therapy and monotherapy. To date, there is no consensus among scientists regarding the effect of combination therapy on serum IFX trough levels.

For pediatric patients, Cheng et al. [14] reported that combination therapy administered for >6 months decreased the risk of sLOR in patients with CD; the same trend was observed in patients with UC, but the results were not significant. These results are consistent with our study; the three patients who continued IFX without sLOR for more than 3 years concomitantly used AZA for >6 months. However, the risk of lymphoproliferative disorders is increasing. Data analysis from the Cancers et Sur-risque Associé aux Maladies inflammatoires intestinales en France study revealed a multivariate-adjusted hazard ratio of 5.28 (p<0.05) for lymphoproliferative disorders in patients who had been administered thiopurines compared with those who had never been administered this agent. Kotlyar et al. [15] conducted a meta-analysis of lymphoma risk in patients with IBD treated with immunomodulators and found that patients aged <30 years had a higher relative risk of lymphoma than older patients. Although the absolute risk was not high in the younger population because of the very low incidence of spontaneous lymphoma, combination therapy in pediatric patients should be used with caution and requires further investigation. Another factor that should be considered is the advent of less immunogenic drugs including GLM. The findings of a study on GLM therapy in adults with moderate-to-severe UC showed lower levels of immunogenicity [16], and comparable results in pediatric patients with UC to adult patients have been reported [17]. If GLM can successfully suppress sLOR and/or IR while retaining the
same level of efficacy as IFX, combination therapy with AZA may not be necessary. Additional data from pediatric patients on long-term maintenance therapy with GLM are needed.

Skin lesions presented as paradoxical psoriasis are a serious complication of long-term IFX therapy. It has been reported that paradoxical psoriasis is more common in patients with CD than in those with UC. Hiremath et al. [18] reported that IFX-induced psoriasis occurred in five of 60 (8.3%) patients with CD and only in one of 15 patients (6.6%) with UC. Courbette et al. [19] reported that 20 of 123 patients (16.6%) with CD developed paradoxical psoriasis and that no patients with UC developed psoriasis. In the present study, 15% of patients developed paradoxical psoriasis. When paradoxical psoriasis can be managed with ointment, IFX can be continued. However, paradoxical psoriasis often becomes resistant to topical treatment and affects children’s faces and scalps [18], which may greatly affect their quality of life; thus, we have considered changing to other biologics.

As described above, IFX is an innovative drug that showed a steroid-sparing effect and maintained long-term remission. However, a considerable number of patients experience PNR, sLOR, and/or IRs during maintenance therapy. In recent years, biologics with different mechanisms of action, including vedolizumab and ustekinumab, have been developed, which have affected physicians’ decision-making about whether to continue IFX or to use other newer biologics, particularly when patients become unresponsive to IFX. However, data on the efficacy and safety of these drugs in children is lacking. Moreover, these new biologics have not been approved for pediatric use anywhere in the world. Careful monitoring of the safety signals associated with long-term maintenance therapy is necessary.

The present study had some limitations. Given that this was a retrospective study conducted in a single tertiary care children’s hospital, selection bias must be considered. Although this study involved a small sample of relatively young patients with severe disease, few reports have described long-term IFX durability for up to 9 years in pediatric patients with UC. In addition, there were no restrictions on the use of concomitant medications, including CS, which may have affected the efficacy assessments. Consequently, patients who required increases in the CS dose were not considered to have achieved a clinical response in this study, even if their PUCAI had improved. To date, Japanese insurance does not cover the measurement of serum IFX concentrations, and IFX dose optimization based on serum IFX levels may contribute to better outcomes.

In conclusion, long-term observation of up to 9 years in this study revealed that IFX is relatively safe and effective in children with UC. Patients who achieved clinical remission with IFX at week 30 sustained long-term colectomy-free IFX treatment, unlike those who failed to achieve clinical remission. In contrast, approximately two-thirds of patients were unable to continue IFX therapy because of PNR, sLOR, IRs, and other side effects such as psoriasis-like skin lesions. Despite these concerns, IFX is an essential drug with pediatric indications and long-term experience, and it remains a key drug for treating children with refractory UC.

REFERENCES

1. Benchimol EI, Fortinsky KJ, Gozdyra P, Van den Heuvel M, Van Limbergen I, Griffiths AM. Epidemiology of pediatric inflammatory bowel disease: a systematic review of international trends. Inflamm Bowel Dis 2011;17:423-39.

https://doi.org/10.5223/pghn.2021.24.1.7
2. 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.

3. Hyams JS, Lerer T, Griffiths A, Pfefferkorn M, Stephens M, Evans J, et al. Outcome following infliximab therapy in children with ulcerative colitis. Am J Gastroenterol 2010;105:1430-6.

4. Hyams J, Crandall W, Kugathasan S, Griffiths A, Olson A, Johanns J, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn’s disease in children. Gastroenterology 2007;132:863-73; quiz 1165-6.

5. Naviglio S, Lacorte D, Lucafo M, Cifì A, Favretto D, Cuzzoni E, et al. Causes of treatment failure in children with inflammatory bowel disease treated with infliximab: a pharmacokinetic study. J Pediatr Gastroenterol Nutr 2019;68:37-44.

6. Birimberg-Schwartz I, Zucker DM, Akriv A, Cucchiara S, Cameron FL, Wilson DC, et al. Development and validation of diagnostic criteria for IBD subtypes including IBD-unclassified in children: a multicentre study from the pediatric IBD Porto group of ESPGHAN. J Crohn’s Colitis 2017;11:1078-84.

7. Levine A, Griffiths A, MARKowitz J, Wilson DC, Turner D, Russel RK, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis 2011;17:1314-21.

8. Turner D, Otley AR, Mack D, Hyams J, de Bruijne J, Uusoue K, et al. Development, validation, and evaluation of a pediatric ulcerative colitis activity index: a prospective multicenter study. Gastroenterology 2007;133:423-32.

9. 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;10:399-9.e1.

10. Takeuchi I, Kaburaki Y, Arai K, Shimizu H, Hirano Y, Nagata S, et al. Infliximab for very early-onset inflammatory bowel disease: a tertiary center experience in Japan. J Gastroenterol Hepatol 2020;35:593-600.

11. Turner D, Ruemmele FM, Orlanski-Meyer E, Griffiths AM, de Carpi JM, Bronsky J, et al. Management of paediatric ulcerative colitis, part 2: acute severe colitis—an evidence-based consensus guideline from the European Crohn’s and Colitis Organization and the European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2018;67:292-310.

12. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn’s disease. N Engl J Med 2010;362:1383-95.

13. Lichtenstein GR, Diamond RH, Wagner CL, Fasanmade AA, Olson AD, Marano CW, et al. Clinical trial: benefits and risks of immunomodulators and maintenance infliximab for IBD-subgroup analyses across four randomized trials. Aliment Pharmacol Ther 2009;30:210-26.

14. Cheng J, Hamilton Z, Smyth M, Barker C, Israel D, Jacobson K. Concomitant therapy with immunomodulator enhances infliximab durability in pediatric inflammatory bowel disease. Inflamm Bowel Dis 2017;23:1762-73.

15. Kotlyar DS, Lewis JD, Beaugerie L, Tierney A, Bresniger CM, Gisbert JP, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. Clin Gastroenterol Hepatol 2015;13:847-58.e4; quiz e48-50.

16. Sandborn WJ, Feagan BG, Marano C, Zhang H, Strauss R, Johanns J, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate-to-severe ulcerative colitis. Gastroenterology 2014;146:85-95; quiz e14-5.

17. Hyams JS, Chan D, Adedokun OJ, Padgett L, Turner D, Griffiths A, et al. Subcutaneous golimumab in pediatric ulcerative colitis: pharmacokinetics and clinical benefit. Inflamm Bowel Dis 2017;23:2227-37.
18. Hiremath G, Duffy L, Leibowitz I. Infliximab-induced psoriasis in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2011;52:230-2.
  PUBMED | CROSSREF

19. Courbette O, Aupiais C, Viala J, Hugot JP, Louveau B, Chatenoud L, et al. Infliximab paradoxical psoriasis in a cohort of children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2019;69:189-93.
  PUBMED | CROSSREF