Short-Term Outcome of Infliximab Therapy in Pediatric Crohn’s Disease: A Single-Center Experience

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Purpose: Studies on the efficacy of infliximab (IFX) in a large population of pediatric patients with Crohn’s disease (CD) are limited, and prognostic factors are not well-known. The aim of this study was to evaluate outcomes of IFX in pediatric patients with CD and to identify factors associated with poor prognosis.

Methods: We retrospectively analyzed medical data of 594 pediatric patients with CD between 1987 and 2013 in a tertiary center. Of these, 156 children treated with IFX were enrolled and were followed up for at least a year with intact data. Outcomes of induction and maintenance, classified as failure or clinical response, were evaluated on the tenth and 54th week of IFX therapy.

Results: We treated 156 pediatric patients with CD with IFX, and the median duration of IFX therapy was 47 months. For IFX induction therapy, 134 (85.9%) patients experienced clinical response on the 10th week. Among the 134 patients who showed response to induction, 111 (82.8%) patients maintained the clinical response on the 54th week. In multivariate analysis, low hematocrit (p = 0.046) at the time of IFX initiation was associated with the failure of IFX induction. For IFX maintenance therapy, longer duration from the initial diagnosis to IFX therapy (p = 0.017) was associated with maintenance failure on the 54th week.

Conclusion: We have shown the acceptable outcomes of IFX in a large cohort of pediatric CD patients in Korea. Hematocrit and early introduction of IFX may be prognostic factors for the outcomes of IFX.

Key Words: Crohn disease, Child, Infliximab

INTRODUCTION

Crohn’s disease (CD) is an immune-mediated inflammatory disease that can develop anywhere in the intestinal tract, and the incidence of pediatric CD is increasing worldwide during recent decades [1]. Previous studies report that the incidence of pediatric CD is 6.6 per 100,000/year, and 19% patients are diagnosed during the first decade of their life [2]. The annual incidence of CD in Asia is also increasing [3]. Corticosteroids, immunomodulators, and anti-TNF therapy have been widely used for treating...
pediatric CD. Each treatment has its own strengths and weaknesses [4], and numerous studies have been published to compare their effectiveness and present guidelines for treatment [5]. Despite higher efficacy of infliximab (IFX) in the treatment of CD, most studies are still based on adult population [6] and data on the efficacy of IFX in pediatric patients with CD are relatively less. Furthermore, there are only a few studies of IFX efficacy which are focused on Asian pediatric CD patients [7-9].

The REACH study is an important study which demonstrated the acceptable efficacy of IFX in children with CD [6]. In addition, recent studies on the initial induction response of IFX in pediatric patients with CD report responses were as good as those in adults [10-13]. Herein, IFX is considered to be effective, showing better outcomes than conventional treatments [11]. However, the efficacy of IFX maintenance after successful induction is still unknown because of minimally available data in children with CD. In a single-center IFX study on pediatric patients with CD, only 41% patients managed to maintain durable remission during a median follow-up of 29 months [14]. Herein, the aims of this study were to evaluate outcomes of IFX induction and maintenance in a tertiary hospital with a large population of pediatric patients with CD and to determine poor prognostic factors related to IFX induction and maintenance therapy.

MATERIALS AND METHODS

Patients

Patients who were diagnosed with pediatric CD at the Seoul Asan Medical Center from January 1987 to December 2013 were retrospectively identified. The diagnosis of pediatric CD was made in children with CD, aged below 18 years, using a multidisciplinary approach based on Porto criteria [15], including clinical symptoms, laboratory tests, radiological images, and endoscopic and histologic evaluations.

Study variables

Patient records were based on patient interviews, conducted at the time of initial hospital presentation. The study was approved by the institutional review board of Asan Medical Center (IRB no. 2017-0764). We collected basic demographics, such as age and sex; clinical characteristics, age at diagnosis, age at first injection of IFX, interval from diagnosis to first IFX injection, behavior and location of disease; and laboratory results when IFX was initiated. The disease behavior and involved locations of CD were defined using Paris classification [16]. Collected laboratory results were serum hematocrit (%), albumin levels (g/dL), C-reactive protein levels (mg/dL), and erythrocyte sedimentation rate (mm/h). Pediatric Crohn’s disease activity index (PCDAI) and Crohn’s disease activity index (CDAI) scores were calculated according to previous protocols [17,18]. Clinical severity was also judged by physician global assessment (PGA) [19].

The schedule of both IFX induction and maintenance was based on the REACH study [6]. IFX was administered at a dose of 5 mg/kg based on the induction and maintenance schedule. The induction schedule involved administration of IFX at 0, 2, and 6 weeks. The maintenance schedule was to administer it every 8 weeks. The outcome was evaluated twice, once on the 10th week of the first injection to evaluate the effects on induction and once on the 54th week of injection to evaluate the effects of maintenance. Outcomes were classified by failure and clinical response; including clinical remission. Patients who failed at induction were excluded from evaluation of outcomes at 54 weeks. Clinical remission was defined as PCDAI lower than 10 or CDAI lower than 150. Clinical response was defined as PCDAI lower than 15 or PCDAI decreasing more than 30 or CDAI decreasing more than 70. Otherwise, the outcome was defined as a failure.

Statistics

Baseline characteristics were described by proportions, means with standard deviations, and medians with ranges. Using logistic regression, we performed both univariate and multivariate analyses to determine prognostic factors related to remission in
both IFX induction and maintenance therapy. Significant risk factors were evaluated by calculating odds ratios (ORs). All prognostic factors with a p-value of < 0.2 in univariate analysis were included in the multivariate analysis. A receiver operating characteristic (ROC) curve analysis with the Youden index was used to find the optimal cut-off point. p-values of < 0.05 were considered to be statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows ver. 23.0 (IBM Co., Armonk, NY, USA).

RESULTS

Baseline characteristics

Data on 594 patients were extracted from computerized medical charts, and 194 patients were found to have been treated with IFX and 191 patients had follow-ups of at least 1 year. Thirty-five patients were excluded; 10 received IFX at another center, 9 received IFX at another center with unclear medical records, 4 could not complete the induction schedule, and 12 had unclear data. Finally, a total of 156 pediatric patients with CD were enrolled in this study (Fig. 1).

The median age at initial diagnosis of the 156 pediatric patients with CD was 15 (range, 13-16) years, and the median age at the start of IFX therapy was 18 (range, 15-21.5) years. The duration from diagnosis to IFX injection was 44.5 (range, 13-92) months. Among these patients, 94 (60.3%) were males and 62 (39.7%) were females. The median follow-up duration was 116 (range, 77.5-169) months (Table 1).

Outcome of IFX induction and maintenance therapy

Twenty-two (14.1%) patients failed during the induction, whereas 134 (85.9%) patients experienced clinical response or remission by the 10th week (Fig. 2). A univariate analysis showed that initial CDAI (p=0.001) and hematocrit (p=0.027) were associated with the response on the 10th week. A multivariate analysis showed that only hematocrit

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**Fig. 1.** Flow diagram of enrolled patients.
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Table 1. Baseline Characteristics of Patients (n=156)

| Characteristic                        | Value                |
|---------------------------------------|----------------------|
| Sex                                   |                      |
| Male                                  | 94 (60.3)            |
| Female                                | 62 (39.7)            |
| Median age at diagnosis (y)           | 15 (2-16)            |
| Median age of IFX first injection (y) | 18 (2-34)            |
| Median interval from diagnosis to IFX injection (mo) | 44.5 (0-236) |
| Initial median PCDAI                  | 40 (15-75)           |
| Initial median CDAI                   | 242 (66-473)         |
| Initial PGA (n=140)                   |                      |
| Mild                                  | 18 (12.9)            |
| Moderate                              | 96 (68.6)            |
| Severe                                | 26 (18.6)            |
| Location at diagnosis                 |                      |
| L1                                    | 14 (9.0)             |
| L2                                    | 11 (7.1)             |
| L3                                    | 131 (84.0)           |
| Behavior at diagnosis                 |                      |
| B1                                    | 134 (85.9)           |
| B2                                    | 18 (11.5)            |
| B3                                    | 4 (2.6)              |
| Hematocrit (%)                        | 35.9 (9.9-46.7)      |
| ESR (mm/h)                            | 40.0 (2-120)         |
| Albumin (g/dL)                        | 3.30 (0.7-5.42)      |
| C-reactive protein (mg/dL)            | 1.72 (0.1-12.1)      |

Values are presented as number (%) or median (range).

IFX: infliximab, PCDAI: pediatric Crohn’s disease activity index, CDAI: Crohn’s disease activity index, PGA: physical global assessment, ESR: erythrocyte sedimentation rate.

(p=0.046, OR, 1.089) was associated with the response on the 10th week (Table 2).

Among the 134 patients who showed response at induction, 23 (17.2%) patients failed to maintain clinical responsiveness and 111 (82.8%) patients maintained clinical responsiveness, including remission, at the 54th week (Fig. 2). A multivariate analysis showed that the duration from diagnosis to IFX injection (p=0.017; OR, 0.990) was associated with the response on the 54th week (Table 2).

Early vs. late introduction of IFX

We analyzed study data to determine if there was a significant between-group difference between early and late injection of IFX (Fig. 3). The ROC curve analysis showed 29 months as a cut-off with an area under the curve of 0.86. Table 3 depicts that patients who had received IFX within 29 months after diagnosis were younger, with a median age of 15 years (p < 0.001) and had a higher PGA severity (38% vs. 2.82%; p < 0.001).

Safety of IFX

Fifteen (9.6%) patients experienced side effects of IFX. Of these, seven (46.7%) patients had immediate infusion reactions, such as rash, tachycardia, hypotension, chest pain, fever, and anaphylaxis. Six (40.0%) experienced infections. Two (13.3%) had myositis and pancreatitis. Of these 15 patients, none had side effects related to malignancy and mortality.

DISCUSSION

In this study, IFX was effective in induction and maintenance in Korean pediatric patients with CD. The proportion of patients who showed clinical responses, which also included clinical remission, was 85.9% and 82.8% for the 10th and 54th week, respectively. This result is similar to previous outcomes in children with CD in Western countries, where 82-88% of study populations responded to IFX therapy [6,14,20,21].

The proportion of patients maintaining remission with IFX generally decreased over time. For example, a study on 120 pediatric patients with CD, with 89% induction rate and 82% maintenance rate at 1 year after IFX, showed a steeply decreasing re-
Table 2. Prognostic Factors of Infliximab Treatment on 10th Week and 54th Week

| Characteristic                       | 10th week Univariate analysis | 10th week Multivariate analysis | 54th week Univariate analysis | 54th week Multivariate analysis |
|--------------------------------------|-------------------------------|---------------------------------|-------------------------------|---------------------------------|
|                                      | OR                            | \( p \)-value                    | OR                            | \( p \)-value                    | OR                            | \( p \)-value                    |
| Sex                                  |                               |                                 |                               |                                 |                               |                                 |
| Male                                 | 1                             |                                 | 1                             |                                 |                                 |                                 |
| Female                               | 0.404                         | 0.053                           | 0.465                         | 0.098                           |                                 |                                 |
| Age of diagnosis (y)                 | 1.057                         | 0.606                           | 1.146                         | 0.268                           |                                 |                                 |
| Age of IFX first injection (y)       | 0.988                         | 0.768                           | 0.938                         | 0.123                           |                                 |                                 |
| Interval from diagnosis to IFX (mo)  | 0.998                         | 0.552                           | 0.992                         | 0.037                           | 0.990                         | 0.017                           |
| Initial PCDAI                        | 0.942                         | 0.175                           | 1.022                         | 0.617                           |                                 |                                 |
| Initial CDAI                         | 0.986                         | 0.001                           | 0.999                         | 0.872                           |                                 |                                 |
| Location at diagnosis                |                               |                                 |                               |                                 |                               |                                 |
| L1                                   | 1                             |                                 | 1                             |                                 |                                 |                                 |
| L2                                   | 0.346                         | 0.414                           | 0.667                         | 0.785                           |                                 |                                 |
| L3                                   | 0.453                         | 0.459                           | 0.361                         | 0.341                           |                                 |                                 |
| Behavior at diagnosis                |                               |                                 |                               |                                 |                               |                                 |
| B1                                   | 1                             |                                 | 1                             |                                 |                                 |                                 |
| B2                                   | 1.322                         | 0.724                           | 0.382                         | 0.108                           |                                 |                                 |
| B3                                   | 0.330                         | 0.376                           | 0.173                         | 0.223                           |                                 |                                 |
| Hematocrit (%)                       | 1.095                         | 0.027                           | 1.089                         | 0.046                           | 1.032                         | 0.460                           |
| ESR (mm/h)                           | 0.994                         | 0.373                           | 0.989                         | 0.150                           |                                 |                                 |
| Albumin (g/dL)                       | 1.247                         | 0.462                           | 1.31                          | 0.364                           |                                 |                                 |
| C-reactive protein (mg/dL)           | 1.030                         | 0.732                           | 0.991                         | 0.908                           |                                 |                                 |

OR: odds ratio, IFX: infliximab, PCDAI: pediatric Crohn’s disease activity index, CDAI: Crohn’s disease activity index, ESR: erythrocyte sedimentation rate.

Fig. 3. Distribution of patients by interval from diagnosis to infliximab (IFX) injection. The median interval from diagnosis to IFX injection was 44.5 (range, 0-236) months, which is indicated by the green line. The optimal cut-off point (29 months), marked by the blue line, was derived from the receiver operating characteristic curve.

A multicenter cohort of 202 pediatric CD patients also showed results of 93%, 78%, and 67% of patients continuing IFX at 1, 2, and 3 years [13].

A recent Canadian multicenter study, between 2008 and 2012, showed a higher rate of good response to IFX in children with CD, with 95.5% and 91% showing 1- and 2-year IFX durability, respectively [12]. However, half of the children in that study used an optimization strategy of dose intensification or interval shortening. Our present study seldom used dose intensification or interval shortening because the Korean government medical coverage guidelines do not allow some modifications for optimization of clinical responses to IFX. Because of the high cost of IFX, the socioeconomic cost must be analyzed for developing a universal optimization strategy for IFX in children who do not show response.

The SONIC study may suggest an efficient and
easy method for maintaining responsiveness to IFX using combination therapy with azathioprine [23]. However, a safety issue of developing lymphoma by combination therapy is still problematic in pediatric patients. Studies of Asian pediatric CD patients are rare, so it is questionable whether the results of IFX efficacy is similar to that of western countries. A nationwide survey in Japan of pediatric CD patients, reported lower remission rates compared to previous studies [9]. Half of the study population was under remission after post-induction, and only 42% went on maintenance therapy. Another study of Korean pediatric CD patients reported that remission was 45% after one year of conventional therapy of IFX [10]. Our study reported higher remission rates of 78.3%, which were similar to previous western studies.

In our study, hematocrit showed a possible association with results by the 10th week, which evaluates the effectiveness of IFX for induction. Previous studies point out that hematocrit can be used as a tool for predicting disease complications and that persistent or recurrent anemia is associated with more aggressive IBD [24,25]. In a recent study, hemoglobin levels were associated with significant improvement with the use of immunomodulators [26]. Bergamaschi et al. [27] showed that in vitro IFX increased erythroid progenitor growth in the peripheral blood of patients, leading to erythropoiesis and improved anemia.

Our study suggested that the duration from diagnosis to IFX injection is associated with maintenance outcomes by the 54th week. The shorter the duration was, the more probable a good outcome was, whereas the OR was too small. Other studies reveal that early introduction of IFX is related with good outcomes and late IFX is associated with greater risks of early surgery [28,29]. A Korean study on 670 adults with CD showed that patients with poor prognostic factors had better outcomes with early introduction of anti-TNF drugs within two years of diagnosis [30]. In addition, a pediatric study on the top-down strategy showed longer remission periods in groups that had early introduction of IFX [10]. However, to date, no data shows that short-term success in the responsiveness to IFX by early introduction reflects long-term outcomes. Because CD is a life-long disease, further studies are needed to elucidate long-term outcomes.

This study has several limitations. First, it is a single-center retrospective study. Second, it did not reflect the results of concomitant treatments, such as steroids and other immunomodulatory agents. Third, the median age of onset of introduction of IFX is 18 years despite the patients with CD in this study having pediatric onsets. Applying to paris classification, four patients were diagnosed CD under age ten, and only one patient started IFX under age ten. Since our patients were under conventional step-up therapy, the median time interval from diagnosis to IFX injection was 44 months, resulting in most of our patients starting IFX at their late adolescence.

In conclusion, we have shown the efficacy of IFX

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### Table 3. Characteristic Differences between Early and Late Introduction of Infliximab Injection Group (n=O)

| Characteristic                  | Early injection | Late injection | p-value |
|--------------------------------|-----------------|----------------|---------|
| Male                           | 35 (64.81)      | 50 (62.50)     | 0.992   |
| Age of diagnosis (y)           | 14              | 15             | 0.191   |
| Age of infliximab first injection (y) | 15              | 21             | <0.001  |
| Severe physical global assessment | 19 (38)         | 2 (2.82)       | <0.001  |
| L3                             | 41 (75.9)       | 71 (88.6)      | 0.137   |
| B1                             | 49 (90.7)       | 66 (83)        | 0.464   |
| Hematocrit (%)                 | 35.8            | 37.0           | 0.137   |
| Erythrocyte sedimentation rate (mm/h) | 45.0            | 37.0           | 0.361   |
| Albumin (g/dL)                 | 3.19            | 3.42           | 0.117   |
| C-reactive protein (mg/dL)     | 2.43            | 1.51           | 0.873   |

Values are presented as number (%) or number only.
in a large cohort of pediatric patients in Korea revealing that the outcomes for IFX durability do not differ from those of other studies. We also proposed that hematocrit may be a prognostic factor for outcomes of IFX induction therapy, and that early introduction of IFX may lead to better outcomes of maintenance.

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