RESEARCH BRIEF

Effect of Infliximab 'Top-down' Therapy on Weight Gain in Pediatric Crohn's Disease

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This retrospective-medical-record review was conducted to evaluate effect of infliximab therapy, particularly with a 'top-down' strategy, on the nutritional parameters of children with Crohn's disease (CD). 42 patients who were diagnosed with Crohn's disease at the Pediatric Gastroenterology center of a tertiary care teaching hospital and achieved remission at two months and one year after beginning of treatment were divided into four subgroups according to the treatment regimen; 'azathioprine' group (n = 11), 'steroid' group (n = 11), infliximab 'top-down' group (n = 11) and 'step-up' group (n = 9). Weight, height, and serum albumin were measured at diagnosis, and then at two months and one year after the initiation of treatment. At 2 months, the *Z*–score increment for weight was highest in the 'steroid' group, followed by the 'top-down', 'step-up', and 'azathioprine' groups. At one year, the *Z*–score increment was highest in 'top-down' group, followed by 'steroid', 'azathioprine', and 'step-up' group. There were no significant differences between the four groups in *Z*–score increment for height and serum albumin during the study period. The 'top-down' infliximab treatment resulted in superior outcome for weight gain, compared to the 'step-up' therapy and other treatment regimens.

Key words: *Children, Crohn's disease, Infliximab, Top-down strategy, Weight gain*.

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Crohn's disease (CD) is characterized by chronic inflammation involving any portion of the gastrointestinal tract, and the inflammation contributes to growth retardation affecting both height and weight [1]. Current practice guidelines recommend that most patients with active disease should initially be treated with corticosteroids [2-4]. Although this approach is usually effective for symptom control, many patients become either resistant or dependent on these drugs [5] or suffer short-and long-term adverse effects. Over the last decade, infliximab, a monoclonal immunoglobulin G1 chimeric antibody directed against tumor necrosis factor-α, has become another therapeutic option for the induction and maintenance of remission in children with severe CD. The efficacy of infliximab suggests that, rather than a progressive course of treatment, early intense ('top-down' strategy) induction may reduce complications associated with conventional treatment and improve quality of life.

The purpose of this study was to perform a comparative evaluation of the effects of infliximab therapy with other treatment modalities, on nutritional parameters for pediatric patients with CD.

METHODS

Among pediatric patients who were diagnosed with CD in accordance with the European Society for Pediatric Gastroenterology, Hepatology and Nutrition - Porto criteria [6] at the Samsung Medical Center between March 2001 and March 2010, we enrolled 42 age-matched patients who achieved remission at two months and one year after initiation of treatment (***Fig.* 1)**. We had a protocol for nutritional evaluation including height, body weight and serum albumin level and applied it in all CD patients. A retrospective chart analysis was conducted by physician notes, laboratory studies, radiology reports, endoscopy records, and histology reports. Patients with severe malnutrition affecting growth and development who required parenteral or enteral nutrition were excluded. This study was approved by our institutional review board.

The patients (n=42) were divided into four subgroups according to the treatment regimen. Eleven patients ('azathioprine' group) were treated with azathioprine and 11 patients ('steroid' group) were treated with oral prednisolone for induction and 11 patients ('top-down' group) were given infliximab from the beginning of

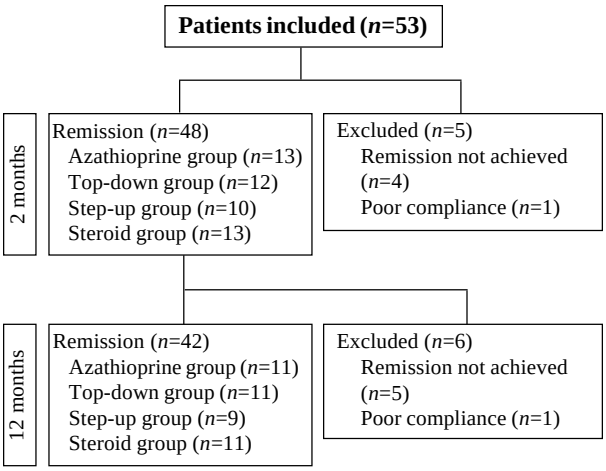

Fig.1 *Diagrammatic flow of the study.*

treatment. Nine patients ('step-up' group) who had been refractory to conventional therapy were treated with infliximab (***Table* I**). Simultaneously all patients were receiving mesalamine (Pentasa, 50-80 mg/kg per day).

In the 'steroid' and 'step-up' group, oral corticosteroids (prednisolone, 1-2 mg/kg per day) were used for induction therapy. Azathioprine (Imuran, 2-3 mg/kg per day) was provided for maintenance therapy as the conventional treatment. In the 'step-up' and 'top-down' group, infliximab (5 mg/kg) was administered by intravenous infusion at weeks zero, two and six, in combination with daily azathioprine, and this course was repeated every eight weeks for ten months thereafter. The group treated with 'top-down' infliximab had not been treated previously with other medications such as corticosteroids or other immunomodulators. All patients were followed for at least 12 months.

PCDAI score is calculated from 11 variables and total score can range from 0 to 100 with higher score indicating greater disease activity. PCDAI scores were measured at diagnosis, and then at two and 12 months after the beginning of treatment. We defined disease remission as a PCDAI score of less than 10 points and relapse as a score greater than 10 points [7,8]. Moderate to severe disease was defined as having a score greater than 30 points. Azathioprine was used for patients with a mild to moderate PCDAI score, and infliximab was used for patients with a moderate to severe score.

Weight and height were measured at diagnosis, and then at two months and one year after the beginning of treatment, except for the 'step-up' group. In the 'step-up' group, weight and height were measured at the beginning of infliximab treatment, and then at two months and one year later.

The *Z* score (standard deviation scores) was used to evaluate and compare anthropometric measurements for CD children of various age and gender. A growth chart for Korean children was used as a reference for body composition.

Statistical analyses were performed using Mann-Whitney U-test for unpaired samples and Wilcoxon signed-rank test for paired samples. Analyses were performed using Kruskall-Wallis test with Bonferroni's correction and Behrens-Fisher method for nonparametric multiple comparisons (SPSS, Chicago, IL, USA). A value of $P < 0.05$ was regarded as statistically significant.

RESULTS

Comparison of baseline parameters in the 4 groups are shown in ***Table* I**. At two months following the start of treatment, in the 'top-down' group, the increment in *Z*-score for weight was superior to those in the 'azathioprine' and 'step-up' group (P=0.010 and P=0.036, respectively). In the 'steroid' group, the increment in *Z* score was also superior to those in the 'azathioprine' and 'step-up' group (P=0.001 and P=0.002, respectively). At one year, in the 'top-down' group, the increment in *Z* score for weight was superior to those for the 'azathioprine' and 'step-up' groups

TABLE I BASELINE PARAMETERS OF THE STUDY POPULATION

	Aza (n=11)	*TD (n=11)*	*SU (n=9)*	*Steroid (n=11)*
Gender, male/female	8/3	8/3	6/3	8/3
Age (y)	15 (11-18)	14 (12-18)	14 (10-16)	14 (11-16)
PCDAI score at diagnosis*	15.0 (5.0-37.5)	37.5 (17.5-55.0)	40.0 (17.5-47.5)	27.5 (12.5-42.5)
at 2 mo	5.0 (0.0-10.0)	2.5 (0.0-12.5)	5.0 (0.0-15.0)	2.5 (0.0-10.0)
at 1 y after beginning treatment	5.0 (0.0-20.0)	0.0 (0.0-10.0)	5.0 (0.0-15.0)	0.0(0.0-20.0)

*All values except gender are median (range); * P=0.001; PCDAI scores after beginning of treatment; PCDAI, Pediatric Crohn's Disease Activity Index; Aza, azathioprine treatment group; TD, infliximab 'top-down' treatment group; SU, infliximab 'step-up' treatment group; Steroid, steroid treatment group.*

WHAT THIS STUDY ADDS?

- 'Top-down' infliximab treatment resulted in superior outcome for weight gain, compared to the 'step-up' therapy and other treatment regimens.

(*P*=0.009 and *P*=0.001, respectively). In the 'steroid' group, the increment in *Z* score was superior to those in the 'step-up' group (*P*= 0.003). At one year, there were no significant differences between the four groups in *Z* score increment for height and serum albumin at diagnosis, or at two months or one year after the beginning of treatment (***Table* II**).

DISCUSSION

One of the critical aims of management in pediatric CD is growth. Malnutrition is a major treatable cause of growth failure in inflammatory bowel disease, with weight loss being present in up to 80% of patients with CD at presentation [9]. Thus, it is essential to evaluate the outcomes of specific therapies in terms of their benefit on growth. To our knowledge, this is the first study to show differences in the improvement in body weight according to treatment regimens. Weight, height, and serum albumin level increased during the treatment period. There was only a significant difference between treatment groups for weight at a year after treatment. For height, the one-year follow-up did not seem to be enough to evaluate linear growth. Serum albumin was restored to a normal level at 2 months in all groups who achieved remission.

Growth failure mostly appears to be due to disease activity, with smaller nutritional and iatrogenic components [10]. The significant difference in weight gain between 'top-down' and 'azathioprine' or 'step-up' group is most likely due to the fact that patients of 'top-down' group were malnourished at baseline because of more severe disease. Infliximab in 'top-down' group led to significant improvement in disease activity and therefore there was marked increase of weight in this group.

At 2 months, 'steroid' group showed the highest z-score increment of weight, which is because steroids generally induce short-term weight gain due to increased appetite. At one year, the 'top-down' group showed the highest *Z* score increment. We assume that the 'step-up' group placed last at one year because the 'azathioprine' group initially included patients with relatively mild to moderate PCDAI score.

The current study was limited in that it was a single-center retrospective study with a small number of patients, and the follow-up period was only one year. We tried to include all patients fulfilling the inclusion criteria; however, selection bias did not disappear completely.

In summary, we found that 'top-down' infliximab treatment resulted in a superior outcome for weight gain, compared to 'step-up' therapy and other treatment regimens. In clinical practice, growth should be carefully considered as an important criterion for management of CD children and an important marker of therapeutic efficiency. Future studies addressing long-term follow-up are needed to determine the efficacy of infliximab treatment.

TABLE II *Z* SCORE INCREMENTS AND ALBUMIN LEVELS IN THE STUDY POPULATION

	Median Z score increments (range)						*Median albumin levels (g/dL) (range)*		
	Weight			*Height*			*Baseline*	*2 months*	*1 year*
	Baseline	*2 months**	*1 year#*	*Baseline*	*2 months*	*1 year*			
Aza	-0.57 (-1.4-2.1)	0.15 (-0.7-0.7)	0.43 (0.0 – 1.5)	-0.25 (-2.0 -1.6)	0.28 (-0.1-0.6)	0.56 (0.0-1.0)	3.8 (1.9 -5.1)	4.1 (3.3-4.6)	4.3 (3.4-4.8)
TD	-0.72 (-2.5-2.0)	0.42 (-0.1-0.6)	0.97 (0.0 – 1.5)	-0.48 (-2.0 -1.0)	0.18 (-0.2-0.5)	0.67 (0.0 -1.5)	3.5 (2.6 -4.6)	4.4 (3.0 -4.9)	4.4 (3.9-5.0)
SU	-0.44 (-1.9-2.2)	0.11 (-0.1-0.5)	0.37 (-0.9 – 0.8)	-0.08 (-1.5-2.3)	0.21 (0.0 -0.4)	0.44 (-0.5-1.4)	3.6 (2.4-4.5)	3.9 (2.9-4.6)	4.0 (3.5-4.6)
Steroid	-0.53 (-1.6-2.0)	0.66 (0.1-0.9)	0.73 (0.1-.5)	-0.18 (-1.8-1.2)	0.34 (0.0 -0.9)	0.54 (0.2-1.6)	3.2 (2.5-4.2)	4.0 (3.7-4.5)	4.1 (3.6 -4.7)

*Aza, azathioprine treatment group; TD, infliximab 'top-down' treatment group; SU, infliximab 'step-up' treatment group; Steroid, steroid treatment group;**

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