

Early Infliximab Yields Superior Long-Term Effects on Linear Growth in Pediatric Crohn's Disease Patients

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See editorial on page 221.

Background/Aims: Information regarding the efficacy of early infliximab treatment in pediatric patients with Crohn's disease (CD) is limited. We aimed to evaluate the impact of early combined immunosuppression on linear growth in pediatric patients with CD by performing step-up comparisons.

Methods: This retrospective study included pediatric patients with moderate-to-severe CD, who received a combination therapy with infliximab and azathioprine for at least 3 years and sustained corticosteroid-free remission without loss of response. The z-scores of the growth indicators obtained at the time of diagnosis and annually for 3 years thereafter were compared between the two groups. **Results:** The early combined immunosuppression group displayed significantly increased linear growth 3 years after diagnosis ($p=0.026$). A significant difference was also observed in the linear growth 3 years after diagnosis between subgroups of Tanner stages 1-2 ($p=0.016$). **Conclusions:** The early introduction of biologics should be considered to improve linear growth in pediatric patients with CD. (*Gut Liver* 2018;12:255-262)

Key Words: Infliximab; Growth; Height; Tanner stage

INTRODUCTION

The conventional approach for treatment of pediatric Crohn's disease (CD) before the recent consensus guidelines of European Crohn's and Colitis Organisation (ECCO) and European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESP-

GHAN)¹ had been constituted of inducing remission with corticosteroid (CS) and maintaining remission with immunomodulators.² Infliximab (IFX) had been considered for those refractory or intolerant to conventional treatment, known as the step-up approach.^{3,4} On the other hand, several clinical trials have introduced the concept of early combined immunosuppression, supporting the early use of IFX and immunomodulators before the use of CS for CD patients with certain high risks.^{5,6}

Data comparing the efficacy of the two approaches on growth of children are limited. In our previous study, no significant differences were found in z-scores for height, weight, and body mass index (BMI) between the two strategies at 3 years after IFX initiation.⁷ In this study, however, patients that had stopped IFX after the first year were also included, resulting in a decline of z-scores for height 3 years after IFX treatment, which is contrary to previous studies.^{3,8-12} Furthermore, the extension to the REACH study (a randomized, multicenter, open-label study to evaluate the safety and efficacy of anti-TNF α chimeric monoclonal antibody in pediatric subjects with moderate-to-severe Crohn's disease)¹³ and recent study by Cameron *et al.*¹⁴ showed better growth improvement in patients under remission, suggesting difference in growth restoration depending on disease control status. Therefore, in order to investigate the long-term effect of combined immunosuppression on linear growth with exclusion of the influence of disease status, we aimed to investigate the impact of early combined immunosuppression on linear growth in pediatric CD patients who had continuously received combined immunosuppression with IFX and azathioprine (AZA) and had sustained remission for 3 years, by comparison with those who had stepped-up to receive combined immunosuppression and had sustained remission for 3 years.

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In addition, we aimed to compare the effect of IFX on linear growth between subgroups of patients further divided according to Tanner stages.

MATERIALS AND METHODS

1. Patient enrollment

This study was a retrospective observational cohort conducted at the Department of Pediatrics of Samsung Medical Center from January 2008 to December 2016. Enrolled patients were those diagnosed with moderate to severe luminal CD with non-penetrating and nonstricturing behavior who had started IFX and AZA before the age of 18. Among these patients, those who had continuously received combined immunosuppression for at least 3 years and had sustained CS-free remission without loss of response (LOR) were included in this study, in order to minimize the effect of unregulated inflammation of CD on growth.

Patients who had stopped IFX before 3 years of treatment, or those who had received dose intensification of IFX due to LOR

were excluded. Patients with previous history of bowel surgery, or IFX indicated for the treatment of refractory perianal fistulas were excluded. The diagnosis of CD was made in accordance with the ESPGHAN-Porto criteria.¹⁵ Moderate to severe luminal CD was defined as a score of 30 points or more on the Pediatric Crohn's Disease Activity Index (PCDAI).¹⁶ Disease classification and behaviour was based on the Paris classification.¹⁷

2. Study design

Since 2008 we have employed a treatment protocol in which patients and guardians were allowed to choose their initial treatment between either a conventional step-up strategy or an early combined immunosuppression strategy in children newly diagnosed with moderate-to-severe CD. After thorough explanation of the pros and cons of each treatment strategy, patients and guardians were given the choice to whether step-up treatment or initiate treatment IFX within 1 month from diagnosis. The investigators did not involve in the decision of which treatment strategy would be initiated.

Table 1. Comparison of Baseline Characteristics in the Two Groups

Characteristic	Step-up (n=16)	Early combined immunosuppression (n=17)	p-value
Male sex	11 (69)	11 (64)	0.806
Tanner stage 1-2 at diagnosis	10 (63)	8 (47)	0.373
Tanner stage 1-2 at IFX infusion	8 (50)	8 (47)	0.866
Lower GI location	16 (100)	17 (100)	0.498
L1	1 (6)	2 (12)	
L2	0	2 (12)	
L3	15 (94)	13 (76)	
Upper GI location	16 (100)	17 (100)	0.208
No involvement	7 (43)	10 (59)	
L4a	2 (13)	2 (12)	
L4b	3 (19)	5 (29)	
L4a+b	4 (25)	0	
Perianal fistula	12 (75)	9 (53)	0.188
Age at diagnosis, yr	12.1 (9.1-15.6)	15.0 (9.9-16.7)	0.009
Age at IFX initiation, yr	14.2 (10.4-16.9)	15.1 (10.0-16.8)	0.407
PCDAI	35.0 (30.0-60.0)	40.0 (30.0-60.0)	0.908
WBC, / μ L	8,455 (4,750-16,220)	8,320 (3,970-13,210)	0.643
Hematocrit, %	33.8 (27.5-39.2)	33.0 (26.0-40.0)	0.928
Platelet count, $\times 10^3$ / μ L	424 (330-672)	378 (287-680)	0.796
ESR, mm/hr	72.5 (45.0-120.0)	69.0 (28.0-99.0)	0.349
CRP, mg/dL	2.2 (0.5-6.2)	2.7 (0.7-7.5)	0.159
Albumin, g/dL	3.6 (2.9-4.5)	3.6 (2.3-4.3)	0.803
Duration from diagnosis to IFX initiation, mo	11.4 (1.5-68.5)	0.7 (0.1-1.0)	<0.001

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

IFX, infliximab; GI, gastrointestinal; L1, distal 1/3 ileum±limited cecal disease; L2, colonic disease; L3, ileocolonic disease; L4a, upper disease proximal to ligament of Treitz; L4b, upper disease distal to the ligament of Treitz and proximal to the distal 1/3 ileum; L4a+b, upper disease involvement in both L4a and L4b; PCDAI, Pediatric Crohn's Disease Activity Index; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Patients in the step-up group received oral CS of 1 mg/kg/day (maximum 60 mg/day) for induction therapy which was tapered over 8 weeks, and oral AZA and mesalazine were provided for maintenance therapy. When the patients in the step-up group proved to be refractory to conventional treatment or dependent to CS, IFX was administered without changes in AZA and mesalazine. IFX was also indicated when clinical relapse was observed during maintenance of clinical remission with AZA and mesalazine. Clinical remission was defined as a PCDAI of 10 points or under, and clinical relapse was defined as a PCDAI of more than 10 points after achieving clinical remission. Patients in the early combined immunosuppression group received intravenous IFX along with oral AZA and mesalazine within 1 month from diagnosis.

In both groups, IFX had been administered with a dosage of

5 mg/kg by scheduled infusion at weeks 0, 2, and 6 during the induction period, and was repeated every 8 weeks thereafter. AZA was initiated at doses of 0.5 to 1 mg/kg/day. The dose of AZA had been modified after initiation when required based on adverse events, laboratory exams, thiopurine methyltransferase genotype results, and thiopurine metabolite levels of 6-thioguanine nucleotides and 6-methylmercaptopurine.^{18,19} Patients in both groups had received partial enteral nutrition (EN) support during the IFX induction phase.

Baseline clinicodemographic characteristics at diagnosis, 1 year, 2 years, and 3 years after diagnosis were obtained in the two groups. Tanner stage at diagnosis, sex, birth date, disease location, and presence of anal fistula and other clinicodemographic data, including PCDAI scores were also obtained. Serum laboratory exams of complete blood cell counts with differential

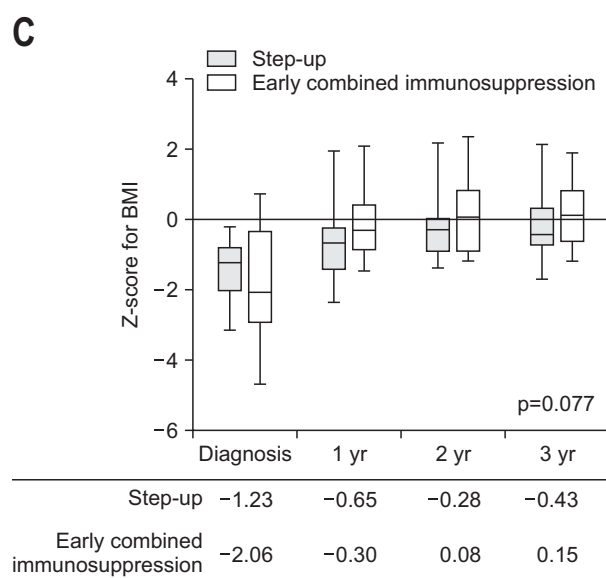
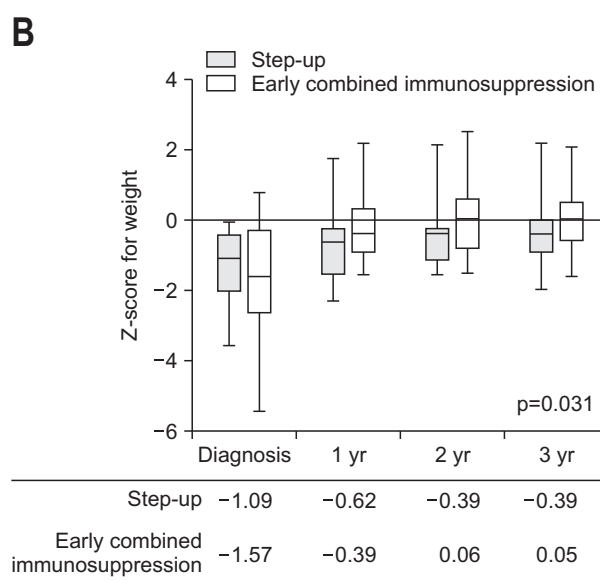
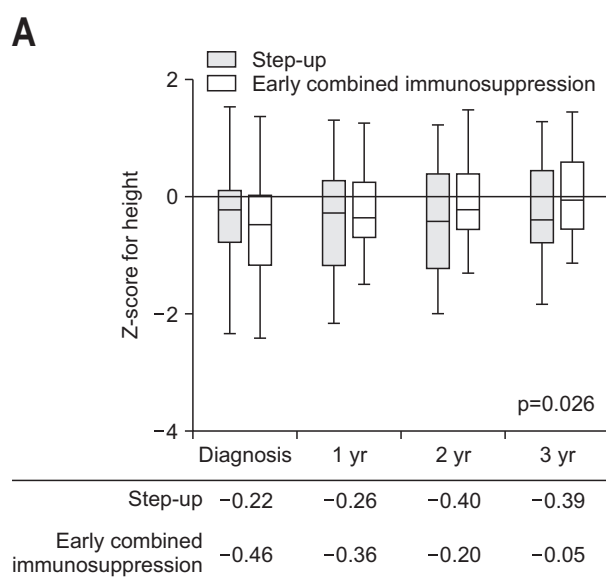


Fig. 1. Box-and-whisker plots of the z-scores of the growth indicators since the time of diagnosis. Box-and-whisker plot of the z-scores of height, weight and body mass index (BMI) showing the median (line in box); 25th and 75th percentiles (box ends) and minimum and maximum (whiskers) values. Height z-scores each year after diagnosis (A); weight z-scores each year after diagnosis (B); and BMI z-scores each year after diagnosis (C). The p-values represent an interaction effect between the treatment strategies and time in the generalized estimating equation analysis. The table below represents the median z-scores of height, weight, and BMI in each group shown in (A), (B), and (C), respectively.

counts, chemistry profiles, erythrocyte sedimentation rate, C-reactive protein were performed on each outpatient visit. PCDAI scores were calculated at each visit to assess the efficacy of treatment. z-scores for height, weight, and BMI were calculated based on the growth charts of the Korea Centers for Disease Control and Prevention.²⁰ z-scores for these growth indicators were compared between the two groups. Analyses between subgroups of patients further divided according to Tanner stages were also conducted. Tanner stages were divided into lower Tanner stage of 1–2 and higher Tanner stage of 4–5 as done in a previous study.¹²

3. Statistical methods

Wilcoxon two-sample test and paired t-test were used for the comparison of continuous variables, based on the results of

Shapiro-Wilk test for normality. Fisher exact test and chi-square test were used for the comparison of categorical variables. Generalized estimating equations (GEE) analysis with unstructured correlation was used to evaluate the time effect and the interaction effect between the two treatment strategies and time on the z-scores for growth indicators. *Post-hoc* comparison and Bonferroni correction were used for multiple comparisons. The p-value for statistical significance was defined as p<0.05. Statistical analysis was carried out on the SAS version 9.3 (SAS Institute, Cary, NC, USA).

4. Ethics statement

This study was approved by the Institutional Review Board of Samsung Medical Center (IRB number: 2015-01-047-002) and was conducted in accordance with the Declaration of Helsinki.

Table 2. GEE Analysis of the z-Scores of the Growth Indicators 3 Years after Diagnosis (n=33)

Factor	Height			Weight			BMI		
	χ^2	DF	p-value	χ^2	DF	p-value	χ^2	DF	p-value
Intercept	0.069	1	0.793	0.068	1	0.794	0.015	1	0.904
Sex	0.260	1	0.610	0.69	1	0.406	1.455	1	0.228
Age at diagnosis	0.168	1	0.682	0.205	1	0.651	0.025	1	0.875
Tanner stage at diagnosis	0.253	1	0.615	0.004	1	0.949	0.243	1	0.622
Treatment strategy	0.626	1	0.429	0.248	1	0.248	0.758	1	0.384
Time	7.621	3	0.055	21.199	3	<0.001	23.855	3	<0.001
Time×treatment strategy	9.270	3	0.026	8.902	3	0.031	6.843	3	0.077

GEE, generalized estimating equation; BMI, body mass index; DF, degree of freedom.

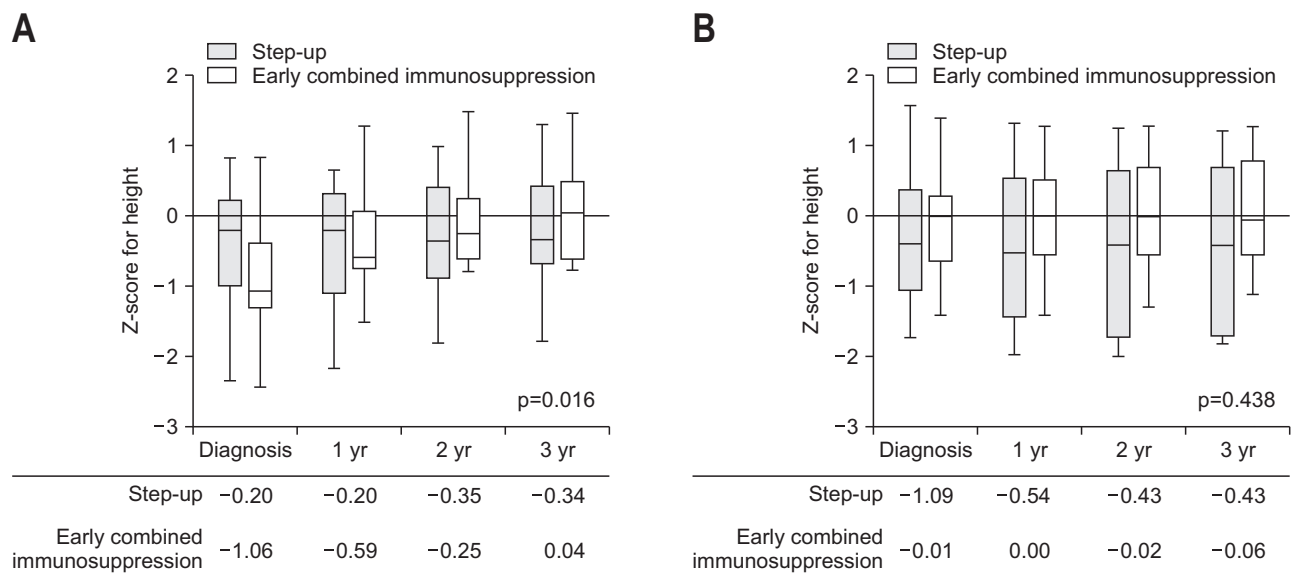


Fig. 2. Box-and-whisker plots of height z-scores since the time of diagnosis in subgroups further divided according to the Tanner stage. Box-and-whisker plot showing the median (line in box); 25th and 75th percentiles (box ends) and minimum and maximum (whiskers) values. Height z-scores of patients in Tanner stages 1–2 each year after the time of diagnosis (A); and height z-scores of patients in Tanner stages 4–5 each year after diagnosis (B). The p-values represent the interaction effects between the treatment strategies and time in the generalized estimating equation analysis. The table below represents the median height z-scores in each group in Tanner stages 1–2 and Tanner stages 4–5 shown in (A), and (B), respectively.

The need for informed consent was waived by the board. And patient's records and information were anonymized and de-identified prior to analysis.

RESULTS

1. Comparison of baseline characteristics between the two groups

A total of 33 patients were included in this retrospective study. Sixteen patients had been allocated to the step-up group, and 17 patients to the early combined immunosuppression group. Median age at diagnosis was significantly lower in the step-up group when compared with the early combined immunosuppression group (12.1 years vs 15.0 years, $p=0.009$) (Table 1). The duration from initial diagnosis to IFX infusion was also significantly longer in the step-up group compared with the early combined immunosuppression group (11.4 months vs 0.7 months, $p<0.001$) (Table 1). As there was no patient identified as Tanner stage 3 at diagnosis, patients were classified as either Tanner stage 1–2 or 4–5 (Table 1).

2. Comparison of z-scores for growth indicators between the two groups

Although median height z-scores from diagnosis showed gradual increase in the early combined immunosuppression group and stayed stable in step-up group, overall distribution of height z-scores failed to show apparent difference between step-up group and early combined immunosuppression group (Fig. 1A). In terms of weight and BMI, better improvements in the median z-score are observed at 1 year after diagnosis in early combined immunosuppression group, but other figures show similar change between two therapeutic strategies (Fig. 1B and C).

GEE analysis enabled further consideration. The effect of treatment strategy on height was not significant when analyzed from diagnosis ($p=0.626$). The effect of time on height was also insignificant when analyzed from diagnosis ($p=0.055$). However, the interaction effect between treatment strategy and time was significant in GEE analysis for z-scores for height ($p=0.026$) and weight ($p=0.031$) starting from diagnosis after adjusting for sex, age at diagnosis, and Tanner stage at diagnosis, suggesting better improvement in z-scores for height and weight in the early combined immunosuppression group than the step-up group (Table 2). Meanwhile, when the z-scores for BMI were analyzed from diagnosis, GEE analysis failed to show a significant interaction effect between treatment strategy and time ($p=0.077$) (Table 2).

3. Analysis in subgroups further divided according to Tanner stage

Height z-scores in subgroups of Tanner stage 1–2 revealed similar height patterns as in Fig. 1, with median height z-scores nearly reaching $z=0$ at 3 years after diagnosis in the early com-

Table 3. GEE Analysis of the z-Scores of Height, Weight and BMI in Subgroups Further Divided According to the Tanner Stage

Factor	GEE analysis of z-scores for height			GEE analysis of z-scores for weight			GEE analysis of z-scores for BMI											
	Tanner stage 1–2 at diagnosis (n=18)	Tanner stage 4–5 at diagnosis (n=15)	Tanner stage 1–2 at diagnosis (n=18)	Tanner stage 1–2 at diagnosis (n=18)	Tanner stage 4–5 at diagnosis (n=15)	Tanner stage 1–2 at diagnosis (n=18)	Tanner stage 1–2 at diagnosis (n=18)	Tanner stage 4–5 at diagnosis (n=15)	Tanner stage 4–5 at diagnosis (n=15)									
	χ^2	DF	p-value	χ^2	DF	p-value	χ^2	DF	p-value									
Intercept	0.334	1	0.563	0.758	1	0.384	0.460	1	0.498	0.116	1	0.734	0.009	1	0.925	0.119	1	0.730
Sex	0.025	1	0.874	0.954	1	0.329	1.556	1	0.212	0.471	1	0.493	1.556	1	0.212	0.471	1	0.493
Age at diagnosis	0.548	1	0.459	0.635	1	0.426	0.561	1	0.454	0.078	1	0.781	0.561	1	0.454	0.078	1	0.781
Treatment strategy	0.202	1	0.653	0.225	1	0.635	0.241	1	0.623	0.189	1	0.664	0.241	1	0.623	0.189	1	0.664
Time	11.163	3	0.011	1.945	3	0.584	11.611	3	0.009	9.856	3	0.020	11.611	3	0.009	9.856	3	0.020
Time×treatment strategy	10.279	3	0.016	2.711	3	0.438	4.618	3	0.202	6.022	3	0.111	4.618	3	0.202	6.022	3	0.111

GEE, generalized estimating equation; BMI, body mass index; DF, degree of freedom.

bined immunosuppression group (Fig. 2). GEE analysis of height z-scores among these patients revealed a significant time effect when analyzed from diagnosis, suggesting improvement of height z-scores overtime after diagnosis regardless of treatment strategies ($p=0.011$). On the contrary, the effect of treatment strategy failed to prove significant results when analyzed from diagnosis, suggesting insignificant difference between treatment strategies in terms of height z-scores ($p=0.653$). The interaction between the treatment strategy and time in z-scores for height when analyzed from diagnosis also proved significant after adjusting for sex and age at diagnosis, indicating better improvement in z-scores for height in the early combined immunosuppression group than the step-up group ($p=0.016$) (Table 3).

In patients with Tanner stage 4–5, GEE analysis of height z-scores failed to prove significant effect in terms of treatment strategy or time when analyzed from diagnosis. Furthermore, the interactions between treatment strategy and time were also insignificant when analyzed from diagnosis (Table 3).

The z-scores for weight or BMI from diagnosis showed similar trends of gradual increase in both treatment groups regardless of Tanner stage. GEE analysis was significant in terms of time regardless of Tanner stage, indicating significant improvement of weight or BMI overtime after diagnosis in both treatment strategies. On the other hand, GEE analysis failed to show significant result in treatment strategy or interactions between treatment strategy and time in terms of weight or BMI (Table 3).

4. Adverse events

No serious adverse event, such as infection or malignancy had occurred in the subjects. Minor adverse events of gastrointestinal disturbance ($n=4$) and hair loss ($n=3$) had occurred in six patients. However, no statistical significance was observed between the two groups ($p=1.000$).

DISCUSSION

This is the first study to compare the efficacy of early combined immunosuppression with step-up treatment strategy in terms of growth for a long-term period of 3 years after diagnosis in pediatric patients with moderate to severe luminal CD who had sustained clinical remission under combined immunosuppression with IFX and AZA. The long-term restoration of linear growth was superior in the early combined immunosuppression when height z-scores were analyzed for 3 years from diagnosis.

While a number of studies support the effect of IFX on growth,^{3,8,9,11,12} there is limited data regarding the effect of early combined immunosuppression on long-term growth restoration. Our study showed that an early combined immunosuppression strategy was superior to step-up strategy in improving long-term height z-scores starting from diagnosis after adjusting for sex, age at diagnosis, and Tanner stage at diagnosis. This significant difference between early combined immunosuppression

and step-up strategy on linear growth was also revealed in a subsequent subgroup analysis of patients with Tanner stage 1–2 after adjusting for sex and age at diagnosis, while no significance was revealed in patients with Tanner stage 4–5. These results indicate that the relative effectiveness of early combined immunosuppression on linear growth may only be expected when growth potential remains, suggesting the efficacy of early introduction of biologics on linear growth restoration in this particular group of pre-pubertal or early pubertal stages.

Growth failure has been recognized as a characteristic feature of pediatric patients with CD for more than 20 years.^{21,22} The degree of growth failure is prominent in patients who are diagnosed with CD in early pubertal stages (Tanner stage 1–2), and those who possess extensive intestinal inflammation at diagnosis.⁹ Moreover, up to 30% of patients continuously have linear growth retardation after treatment.²³ Although the etiology of growth failure in CD remains unclear, several factors have been proposed to be interrelated with growth failure, while the two most important factors are chronic undernutrition and inflammatory cytokines secreted from the inflamed intestine.^{23–25} The long term use of CS, one of the conventional mainstays in CD, also increases the risk for growth failure.²²

The 2014 ECCO/ESPGHN guideline recommends exclusive EN for at least 68 weeks instead of CS as the first choice for induction in pediatric CD patients.¹ The primary induction with IFX is considered for patients with high risk factors including deep colonic ulceration on endoscopy, extensive (pan-enteric disease), marked growth retardation of > -2.5 height z-score, severe osteoporosis, stricturing and penetrating disease at onset, or severe perianal disease.¹ While most previous cohorts have failed to reveal a restoration of height to a normal distribution, one recent study including luminal CD patients treated with IFX showed a restoration of height z-scores to near normal levels of $z=0$ when IFX was introduced earlier during the disease course.¹² Although our study differs in factors such as disease severity at diagnosis, the criteria for patient inclusion, and group division, our findings correspond with the findings of Church *et al.*,¹² showing a restoration of height to a normal level of $z=0$ in patients of the early combined immunosuppression group with Tanner stage 1–2. Combining the findings of our study with Church *et al.*¹² and considering the unsatisfying compliance to exclusive EN that many physicians face in real-life clinical practice, we propose that on addition to initial exclusive EN treatment, biologics should be considered when continuous linear growth failure is noted in CD patients of Tanner stage 1–2.

The main role of AZA in combination therapy seems to be involved in the suppression of antibodies against IFX, which seems to benefit for 6 months to 1 year from treatment initiation.²⁶ However, serious complications including infection or lymphoma such as hepatosplenic T-cell lymphoma (HSTCL) may complicate the use of AZA, especially in young males.^{27,28} These observations have led to a decrease in use of AZA among

pediatric CD patients and methotrexate (MTX) has been widely used instead of AZA. However, there is scarce data regarding MTX usage in combination treatment. One randomized double-blinded, placebo-controlled study failed to prove the additional benefit of combination therapy with IFX and MTX in comparison with IFX monotherapy.²⁹ A recent review on the benefits and risks of combined immunosuppression therapy in pediatric IBD suggested that the usage of combination therapy may be indicated in patients having high risk of serious disease-related complications, while emphasizing the importance of a personalized strategy, aiming at balancing the risk and benefit, until more evidence accumulates in children.³⁰

Our study possesses some limitations. First, the small number of subjects may not represent the actual patient population in real life practice. Second, the inclusion criteria may have posed a risk for selection bias. Long-term use of IFX and the sole inclusion of subjects who were under sustained clinical remission may have affected the analysis by selecting a subgroup of patients who responded well to treatment. Moreover, inclusion of only those who were under sustained clinical remission without consideration of endoscopic remission only partially eliminates the effect of inflammation on growth, as a discrepancy between clinical symptoms and endoscopic findings exists during IFX treatment.³¹ Third, the younger age at diagnosis in the step-up group may have contributed to a higher growth potential in the step-up group, possibly neutralizing the effect of early combined immunosuppression on linear growth. However, despite this significant difference in diagnosis age, Tanner stage did not show a significant difference between the two groups. This may have been due to the delay of puberty in pediatric CD.³¹ Moreover, despite the possible neutralizing effect due to the difference in age between groups, statistical significance was revealed between the two groups. Fourth, analysis regarding adverse events of early combined immunosuppression was limited in our study. Due to the intrinsic design of our study to include patients tolerable to long term use of IFX for 3 years, no major side effects were noticed during the observation period regarding combined immunosuppression. However, to date we have not experienced any life-threatening side effects including HSTCL or any malignancies.³² Further studies excluding the limitations in our study should allow more precise evaluation regarding the effect of early combined immunosuppression on linear growth.

In conclusion, although linear growth rate was similar between the early combined immunosuppression and the step-up group during the period of combination treatment, long-term restoration of linear growth was superior in the early combined immunosuppression when compared from diagnosis. This difference was also significant in patients in Tanner stage 1–2 at diagnosis. Early introduction of biologics at diagnosis should be considered in terms of improvement of linear growth in pediatric CD patients with Tanner stage 1–2.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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