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Differences in Outcomes Over Time With Exclusive Enteral Nutrition Compared With Steroids in Children With Mild to Moderate Crohn's Disease: Results From the *GROWTH CD* Study

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Abstract

Background: Exclusive enteral nutrition [EEN] and corticosteroids [CS] induce similar rates of remission in mild to moderate paediatric Crohn's disease [CD], but differ with regard to mucosal healing. Our goal was to evaluate if EEN at diagnosis was superior to CS for improving long-term outcomes.

Methods: We prospectively followed newly diagnosed children aged < 17 years, with mild to moderate CD at baseline, for 2 years in the *GROWTH CD* study. Patients were evaluated at baseline and at 8, 12, 78, and 104 weeks. Remission, relapses, complications [fibrostenotic disease, penetrating disease, and active perianal disease] and growth were recorded throughout the study. A propensity score analysis was performed.

Results: A total of 147 children [mean age 12.9 ± 3.2 years], treated by EEN [$n = 60$] or CS [$n = 87$] were included. New complications developed in 13.7% of CS [12/87] versus 11.6% of EEN [7/60],

p = 0.29. Remission was achieved in 41/87 [47%] in CS and 38/60 [63%] EEN, p = 0.036. Median time to relapse did not differ [14.4 ± 1 months with CS, 16.05 ± 1.1 EEN, p = 0.28]. Mean height Z scores decreased from Week 0 to Week 78 with CS [-0.34 ± 1.1 to -0.51 ± 1.2, p = 0.01], but not with EEN [-0.32 ± 1.1 to -0.22 ± 0.9, p = 0.56]. In a propensity score analysis, EEN was superior to CS for inducing remission [p = 0.05] and trended to superiority for height Z score [p = 0.055].
Conclusions: Use of EEN was associated with higher remission rates and a trend toward better growth but with similar relapse and complication rates in new-onset mild to moderate paediatric CD.

Key Words: Crohn; inflammatory bowel disease; child; diet; steroids; enteral nutrition; relapse; growth; complications

1. Introduction

The goals of therapy in inflammatory bowel diseases include induction of remission and prevention of complications. Most decisions regarding use of medications at disease onset rely on ability to induce remission or maintain remission rather thaability to prevent complications. Current ECCO/ESPGHAN guidelines[1] recommend using exclusive enteral nutrition [EEN] for 6–8 weeks (with or without an immune modulator [IMM]) as the initial induction of remission therapy in mild to moderate active Crohn's disease [CD]. This was based on clinical studies[2–4] demonstrating high remission rates with a decline in inflammatory markers, as well as a meta-analysis[5–7] demonstrating that EEN was equivalent to corticosteroids [CS] for induction of remission, but with fewer side effects. However, recent reports have demonstrated high remission rates but also a high relapse rate during the first year of therapy.[8,9]

Recent studies have demonstrated that EEN may not only induce high rates of remission but may be associated with superior mucosal healing and normal C-reative protein [CRP] remission.[2,5,6,10–13] We thus hypothesised that use of EEN in mild to moderate CD would be associated with a decreased risk for relapse and early complications. Our goal was to evaluate the outcomes of patients with mild to moderate disease at presentation, in an inception cohort from the *GROWTH CD* study, treated with either EEN or CS, in order to evaluate if early use of EEN might reduce early complication rates and improve growth.

2. Methods

2.1. Patient population

The *GROWTH CD* study was a prospective inception cohort that followed newly diagnosed treatment-naïve children with CD, conducted among 17 sites in Europe and Israel, from the Paediatric IBD Porto Group of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition [ESPGHAN] and supported by the European Crohn's Colitis Organisation [ECCO]. The patient population of the present research consisted of consecutive patients with mild to moderate disease, enrolled in the prospective ***G**rowth **R**elapse and **O**utcomes With **TH**erapy CD [GROWTH CD]* study [NIH NCT00711945]. This framework study was designed to evaluate and prognosticate different early adverse patient outcomes, such as growth retardation, relapse, complicated disease behaviour, and requirement for surgery, from the first remission, and to evaluate the role of treatment choices on these outcomes. This study was planned a priori to evaluate outcomes related to induction of first remission and the effect of initial therapy on these outcomes, and to evaluate relapse by 78 weeks [early relapse] and complications and surgery by 104 weeks [early complications]. Height Z score at baseline and at Week 78 was calculated using US Centers for Disease Control and Prevention [CDC] Z scores adjusted for gender.[14] The 78-week outcome was chosen to reflect an adequate time window for relapse, assuming that patients who did not relapse by this time were at low risk.

The study evaluated children 4–17 years of age between 2010 and 2013. In order to emphasise points regarding enrolment, follow-up, therapy, and data entry during the study, two investigators' meetings were held: in Madrid in 2009 and in Porto in 2010. Patients were seen at scheduled visits at Week 0 [diagnostic visit], and Weeks 8, 12, 26, 52, 78, and 104 thereafter. Inclusion criteria required a diagnosis of Crohn's disease by a combination of clinical, laboratory, endoscopic, and histological criteria[15] following colonoscopy, gastroscopy, and small bowel imaging. All centres obtained ethical approval, and written consent was obtained from all participants. Patients were subsequently classified by the Paris classification[16] using the location and behaviour of disease from the baseline to the Week 12 visit. In the present study, we included only children with mild-moderate disease who were initially treated with either EEN or steroids to induce remission at diagnosis.

Active disease was defined as a Paediatric Crohn's Disease Activity Index [PCDAI] ≥ 10. Mild to moderate disease was defined as PCDAI > 10 < 40. Steroid-free remission at Week 12 was used to predict long-term outcomes and also to assess the effect of the induction therapy. Remission for this study was rigorously defined by physician's global assessment [PGA] coupled with a PCDAI < 10 at Week 12.

Induction treatment for patients enrolled in to the GROWTH CD study was standardised for all included patients per protocol. Patients could have received any steroid treatment [prednisone or methylprednisolone 1–1.5 mg/kg /day to be tapered by Week 11], EEN with any formula but exclusively for 6–8 weeks, as well as biologics, antibiotics, and mesalamine. Steroids were to be weaned by Week 12 and those requiring steroids past this time point were considered steroid dependent. Patients included in this study were only those who received EEN or CS at diagnosis.

Patients could have commenced on IMM at standardised doses of mercaptopurine [1–1.5 mg/kg/day], azathioprine [2–2.5 mg/kg/day], or methotrexate [15 mg/m^2,week] according to the physician's discretion. Early use of IMM was defined as use within the first 8 weeks of disease.

Explicit clinical and therapeutic data were collected at each visit through Week 78 on standardised case report forms. At each visit a PCDAI was calculated and CRP was obtained [registered in mg/dL]. Calprotectin was collected at baseline. Normal CRP was defined as CRP < 0.5 mg/dL [< 5 mg/L]. An additional visit at 104 weeks was performed to capture complications, surgery, and sustained remission. Repeat colonoscopies and imaging to detect complications were performed according to physicians' discretion.

The primary endpoint was complication rate through Week 104. Secondary endpoints included steroid-free remission at Week 12, relapse rates by Week 78, time to relapse, and growth by Week 78. Complications were defined as stricturing disease [based on endoscopy, surgery, or imaging demonstrating pre-stenotic dilatation], penetrating disease, or active perianal disease defined as discharging fistula or abscess. Other perianal findings were not considered complications. Surgery was defined as any surgical procedure for an inflammatory bowel disease [IBD]-related complication.

In order to have rigorous associations, we defined remission as PCDAI < 10 obtained from the original therapy, such that if patients required additional therapy before Week 12 they were considered failing to obtain remission on the original therapy. Height Z score was not incorporated in the PCDAI score for remission at Week 12, since it is not responsive immediately to clinical remission.

We performed a second predetermined analysis among patients who entered remission [to exclude patients who did not obtain remission with their original therapy] and subsequent development of complications. For this second analysis, inclusion criteria included: baseline PCDAI 12.5–37.5; presenting with inflammatory behaviour [B1] and no active perianal disease [defined as draining fistula or abscess]; and in remission at Weeks 8 and 12 with 6–8 weeks of EEN or with CS 1–1.5 mg/kg prednisone [with or without concomitant IMM]. This cohort was chosen to evaluate if there are differences between therapies if patients successfully obtain remission, to reduce confounding factors, and to evaluate new-onset complications that were not present at diagnosis.

2.2. Statistical analysis

Data were stored on Excel spreadsheet and analysed on SPSS statistical analysis software [IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. 2016]. Data are described as mean and standard deviation [SD] or median and interquartile range [IQR], according to the distribution of the data. Continuous data were compared by treatment using the Student's t-test for independent samples or the Wilcoxon rank sum test, as appropriate. Categorical data were compared by treatment, using the chi square or Fisher's exact tests as appropriate, and the McNemar test for paired data from matching. For patients with missing data from Week 12, we imputed the last observation carried forward. Any change in therapy was imputed as a failure of the previous therapy. Intention-to-treat analysis was performed using the baseline visit for therapy, and the per-protocol analysis used the medication that actually induced remission, in order to evaluate the long-term outcome of the drug used for remission. The Kaplan–Meier estimator was used to evaluate the time for relapse. Log rank test was used to compare relapse between patient groups. Mean time to relapse was used, as the median was not achieved within the time evaluated. Additional analysis using a propensity score was used to confirm outcomes if there were differences between groups at baseline. All tests were two-sided and considered significant at $p < 0.05$.

Since there were significant differences in baseline characteristics between the two study groups, a propensity score matching was performed to confirm the results; it was calculated using multivariate logistic regression. Variables included in the logistic regression were age, gender, baseline PCDAI, and use of IMM by Week 12, and variables paired included also disease location by the Paris classification and inflammatory markers.

The propensity score was calculated as the probability of treatment with EEN, using logistic regression which included three baseline characteristics that differed between groups at a level of $p \leq 0.1$: PCDAI, IMM, and age, which were used for matching. A difference up to 5% was considered acceptable for matching. After matching, the groups were compared using the McNemar test for categorical variables and the paired simple t-test or Wilcoxon signed test for continuous variables. Multivariate conditional logistic regression was used to identify predictors for study outcomes. All tests were two-sided and considered significant at $p < 0.05$.

3. Results

3.1. Demographic data

Among 285 enrolled patients [range PCDAI 2.5–75], with long-term follow-up and valid baseline and induction visits included in the GROWTH cohort, we identified 147 with mild to moderate disease who had received either EEN [$n = 60$] or CS [$n = 87$] for induction of remission [Figure 1]. Among patients excluded, 97/285 [34%] patients had severe disease [PCDAI ≥ 40]. The remaining 41 patients were excluded because they did not receive CS or EEN or because of use of combinations of therapy at baseline [EEN+ antibiotics, CS+ antibiotics, EEN+CS, CS+ biologic, etc.]. Demographic data are presented in Table 1.

At baseline, the steroid group received more IMM by Week 8 and had slightly higher but significant median PCDAI score. Among CS patients treated with IMM, thiopurines were used in 73/76 [96%] patients and methotrexate in three [3.9%]. Among 42 patients treated with EEN and IMM, 37 [88.1%] were treated with thiopurines and five [11.9%] were treated with methotrexate. Baseline PCDAI did not differ between patients receiving or not receiving IMM: patients with IMM 28.75 [IQR 22.5–35], without IMM 25 [IQR 18.75–32.5], $p = 0.081$, nor did baseline calprotectin: calprotectin with IMM 1800 [IQR 600–1800], calprotectin without IMM 1495 [IQR 233–1800], $p = 0.365$.

3.2. Outcomes based on use of EEN or CS

During follow-up, 19 patients developed 22 new events deemed complications, and one reported that stricture at baseline was non-existent by 2 years. Seven patients [4.7%] developed a new perianal

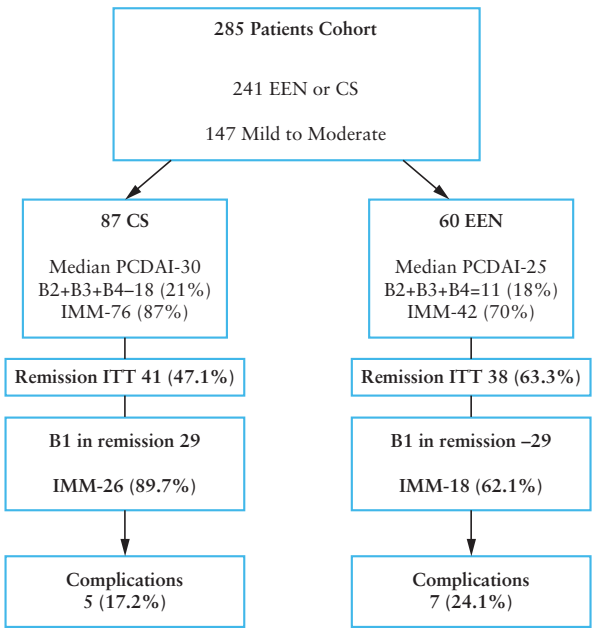

Figure 1. Consort diagram.

Table 1. Demographic data intention-to-treat [ITT] analysis.

	EEN [*n* = 60]	CS [*n* = 87]	Total [*n* = 147]	*p*-Value
Age [years]	12 ± 3.1	13.5 ± 3.1	12.9 ± 3.2	0.005
Gender: male	36 [60%]	59 [67.8%]	95 [64.6%]	0.25
PCDAI Week 0 [median][IQR]	25 [17.5–32.5]	30 [25–35]	27.5[22.5–35]	0.004
Tanner				
Z score Week 0	-0.318 ± 1.1	-0.345 ± 1.1	-0.334 ± 1.2	0.890
CRP Week 0 [mg/dl] [median][IQR]	2.03 [0.85–4.23]	2.61 [0.7–4.43]	2.45 [0.82–4.36]	0.508
Calprotectin [µg/g] [median][IQR]	1800 [940–1905]	1687 [389–1800]	1800 [600–1800]	0.139
IMM	42 [70%]	76 [87%]	118 [80%]	0.009
Behaviuor				
B1	48 [80%]	69 [79%]	117 [80%]	0.574
B2	3 [5%]	12 [13.8%]	15 [10%]	
B3	0	1 [1.2%]	1 [1.4%]	
B2, B3	0	0	0	
Location				
L1	19 [32%]	21 [24%]	41 [27%]	0.192
L2	1 [1.7%]	7 [9.2%]	8 [5.3%]	
L3	38 [63.3%]	55 [63.2%]	97 [64%]	
L4a	19 [32%]	41 [47%]	60 [41%]	0.236
L4b	9 [15%]	11 [12.6%]	20 [14%]	
L4a + L4b	9 [15%]	8 [9.2%]	17 [11.6%]	

EEN, exclusive enteral nutrition; CS, corticosteroids; PCDAI, Paediatric Crohn's Activity Disease Index; IQR, interquartile range; CRP, C-reactive protein; IMM, immunomodulators.

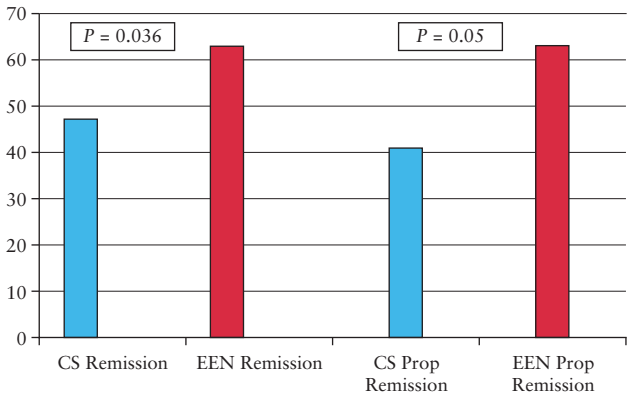

Figure 2. Remission by therapy, intention-to-treat [ITT], *n* = 285, univariate analysis; and remission by propensity score matching, *n* = 92.

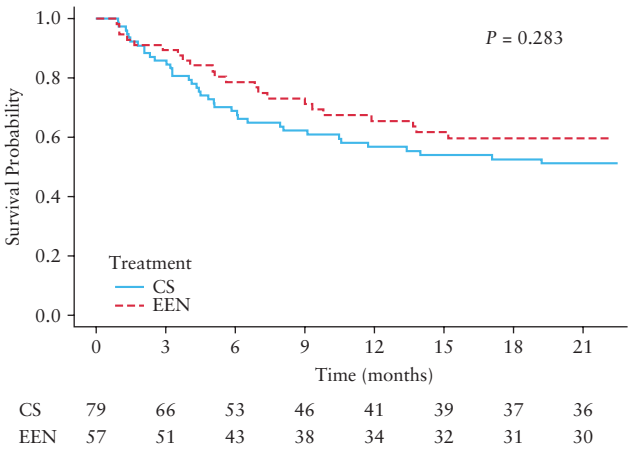

Figure 3. Mean time to relapse for corticosteroid [CS]- and exclusive enteral nutrition [EEN]-treated patients using log rank test.

abscess or discharging fistula, 11 developed a stricture [7.5%], and three [2%] reported penetrating disease. Nine new events occurred in patients with a pre-existing complication. In a univariate analysis, new complications by 2 years were not statistically significant between groups—CS: 12/87 [13.7%]; EEN: 7/60 [11.7%]; $p = 0.29$.

Surgical procedures for complications were performed in 5.4% [10/147] of patients by Year 2, 9.2% [8/87] among CS- and 3.3% [2/60] in EEN-treated patients, $p = 0.164$. EEN was significantly superior to CS to induce remission: CS: 41/87 [47%]; EEN 38/60 [63%]; $p = 0.036$; Figure 2]. Relapse rates by 78 weeks were similar between CS [43/87, 49%] and EEN [27/60, 45%; $p = 0.552$]. Median time to relapse was not reached for either group by 78 weeks [mean time to relapse for CS-treated patients 14.39 ± 1 months and for EEN 16.05 ± 1.1 months, $p = 0.283$ log rank test]. Time to relapse using Kaplan-Meier curves is portrayed in Figure 3.

Use of biologics between Weeks 12 and 104 was significantly higher among patients treated with CS compared with those treated initially with EEN—CS 16/87 [18.4%]; EEN 4/60 [6.7%]; $p = 0.042$—even though there was no difference in time to relapse or the relapse rate. Baseline severity as determined by baseline PCDAI and CRP levels for patients who required a biologic within 78 weeks [PCDAI: 27.5, IQR 25–32; CRP: 2.9, IQR 1.6–5] did not differ from those who did not receive a biologic [PCDAI: 27.5, IQR 20–35; CRP: 2.3, IQR 0.7–4.3; $p = 0.874, 0.145$, respectively].

Baseline PCDAI for patients developing complications [27.5, IQR 25–35] did not differ from patients who did not develop complications [27.5, IQR 20–35; p = 0.109]. Moreover, among CS-treated patients, baseline PCDAI for patients developing complications [30, IQR 26.25–36.25] versus PCDAI for patients who did not develop complications, did not differ [30, IQR 22–35; $p = 0.517$]. The use of IMM did not significantly differ with regard to relapse rate: 13/30 [43%] without IMM; 52/117 [44%] with IMM; $p = 0.970$, complication rate: 8/30 [27%] without IMM; 30/117 [26%] with IMM; $p = 0.850$] and the need of biologic treatment: 2/30 [6.7%] without IMM; 18/117 [15%] with IMM; $p = 0.240$].

Table 2. Basic characteristics of EEN and CS pairs matched by baseline PCDAI score, baseline use of IMM and age.

	Matched EEN [*n* = 46]	Matched CS [*n* = 46]	*p*-Value
Age [years]	12.39 ± 2.97	12.28 ± 3.16	0.848
Gender: male	27 [58.7%]	30 [65.2%]	0.664
PCDAI Week 0 [median][IQR]	25 [20–32.5]	27.5 [20–32.5]	0.328
Z score Week 0	-0.25 ± 1.1	-0.62 ± 1.3	0.156
CRP Week 0 [mg/dl] [median][IQR]	2.03 [0.90–4.31]	2.10 [0.62–3.40]	0.767
Calprotectin [µg/g] [median][IQR]	1300 [389–1800]	1800 [364–1815]	0.629
IMM	37 [80.4%]	35 [76.1%]	0.774
Behaviour			
B1	36 [78.3%]	38 [82.6%]	0.587
B2	9 [19.6%]	8 [17.4%]	
B3	1 [2.1%]	0	
Location			
L1	15 [32.6%]	6 [13%]	0.298
L2	0	4 [8.7%]	
L3	27 [58.7%]	32 [69.6%]	
L4a	15 [32.6%]	23 [50%]	0.473
L4b	6 [13%]	8 [17.4%]	
L4a + L4b	7 [15.2%]	4 [8.7%]	

EEN, exclusive enteral nutrition; CS, corticosteroids; PCDAI, Paediatric Crohn's Activity Disease Index; IQR, interquartile range; CRP, C-reactive protein; IMM, immunomodulators.

Mean height Z scores deteriorated from Week 0 to Week 78 in the CS group [Week 0: -0.345 ± 1.1; Week 78: -0.508 ± 1.2; p = 0.01], but not in the EEN group [Week 0: -0.318 ± 1.1; Week 78: -0.225 ± 0.9; p = 0.56]. Evaluation of mean height Z scores for patients with Tanner 1–3 at diagnosis revealed a similar pattern. Mean height Z score for patients treated with EEN remained stable [from -0.36 ± SD at baseline to -0.34 ± SD at Week 78; p = 0.63], whereas patients treated with CS suffered a decline in Z scores [from -0.62 ± SD at baseline to -0.788 ± SD; p = 0.039].

Upon multivariate analysis, steroid-free clinical remission remained superior with EEN [p = 0.026]. In a multivariate regression model adjusted for age, baseline CRP, baseline PCDAI, and disease behaviour [using the Paris classification], choice of treatment was not associated with development of complications by Week 104 [p = 0.29] or with use of biologics. In a further multivariate regression model adjusted for age, gender and disease behaviour, choice of treatment was not associated with surgery [p = 0.185]. Similarly, treatment type was not associated with relapse by Week 78, as appeared at a multivariate regression adjusted for age, gender, and baseline PCDAI [p = 0.811].

3.3. Propensity-paired samples analysis for outcomes based on therapy

Using the propensity score, 46 matched pairs were obtained. Baseline characteristics after matching were not significantly different between treatment groups [Table 2]. EEN was superior for remission at 29/46 [63%] relative to CS at 19/46 [41%]; p = 0.05 [Figure 2]. Baseline height Z score did not differ between groups [CS: -0.62 ± 1.3; EEN: -0.25 + 1.1; p = 0.156]; however, height Z score for the CS group decreased over time whereas it remained stable for the EEN group. By Week 78 there was a nearly significant trend towards significance, with higher Z scores favouring the EEN group [CS: -.763 ± 1.3 SD; EEN: -0.226 ± 1 SD; p = 0.055]; this appears in Figure 4. Relapse by Week 78 with CS: 24/46 [52.2%]; EEN: 24/46 [43.5%], complications with CS: 12/46 [26.1%]; EEN: 9/46 [19.6%], and surgery with CS: 4/46 [8.7%]; EEN: 2/46 [4.3%] by Week 104 did not differ [p = 0.541, 0.648, 0.688, respectively] between treatment types.

3.4. Does treatment make a difference if remission is present?

We subsequently focused our attention on patients with B1 and no perianal [fistula or abscess] disease entering steroid- and biologic-free remission on either therapy, by excluding patients from the same cohort who failed to obtain remission solely with CS or EEN [Figure 1]. Demographic data for this per-protocol remission cohort for analysis are presented in Table 3.

We had 58 patients who obtained steroid-free remission of PCDAI < 10 with EEN or steroids. Relapse rate within 78 weeks was equal between groups at CS: 9/29 [31%]; EEN: 10/29 [34.5%]; p = 0.851]. New complications developed in 12/58 [20.7%] of patients [seven active perianal fistula, two abscess, 5 five stricture], and did not differ between CS at: 5/29 [17.2%] and EEN at: 7/29 [24.1%]; p = 0.561. Only one patient from this cohort required surgery [from the CS group].

4. Discussion

This is the first prospective study, to our knowledge, to compare long-term outcomes of therapy, comparing EEN with CS [with or without IMM] as a first-line therapy in mild to moderate CD. Clinical remission is no longer the only goal of therapy. Goals of therapy are sustained clinical remission, prevention of complications, and surgery. Mucosal healing has been associated with these goals, leading this to be an endpoint in clinical studies instead of the patient outcomes it is supposed to generate. Although we hypothesised that the superior mucosal healing and normal CRP remission that have been associated with EEN in other studies would decrease complications and surgery [the primary endpoints], we did not find this to be the case. Complications, time to relapse, and surgery rates did not differ between groups with multivariate analysis or with a propensity score analysis.

However, there appeared to be two treatment advantages associated with EEN. EEN was associated with superior clinical remission rates even after correcting for confounders such as baseline severity and use of IMM, with a propensity score analysis. This superior remission rate did not translate, however, into lower relapse, or

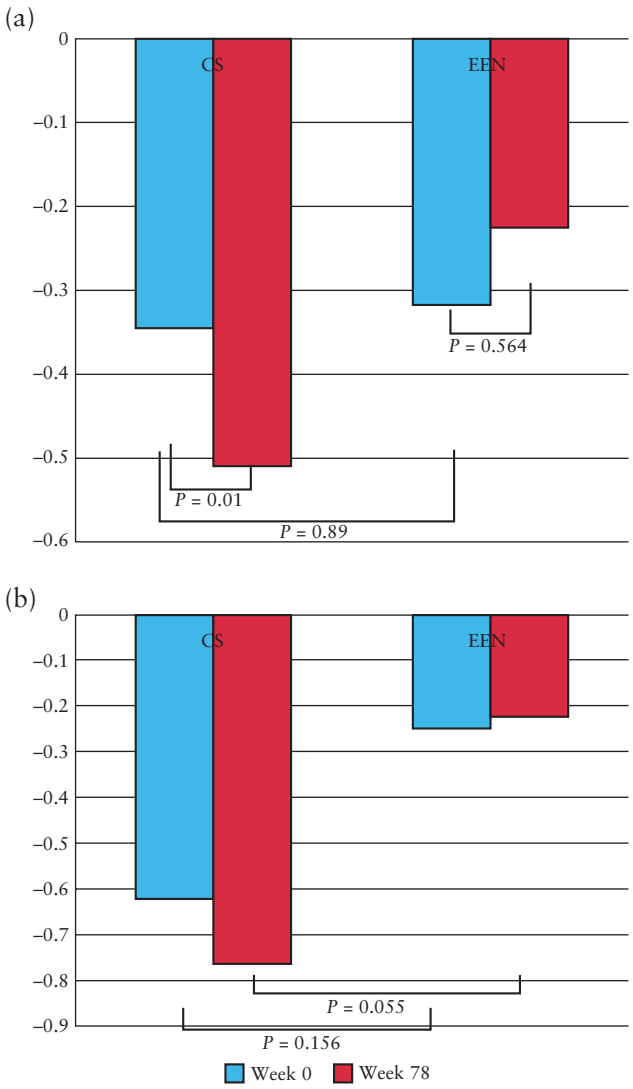

Figure 4. Height Z score. [A] intention-to-treat [ITT]; [B] propensity score matching. Univariate analysis, blue bar represents baseline height Z score, red bar represents height Z score at Week 78.

complication rates, or biologic use, with multivariate analysis. We did not demonstrate that one group was more likely than another to require biologics in the propensity score analysis. Theoretically, patients who are not in steroid-free remission are more likely to have relapse or complications because of uncontrolled disease and inflammatory activity. However, failure to achieve CS-free remission may have led to use of additional therapy which was effective for remission, and thus there was no difference in relapse. We performed an analysis of patients in both groups in steroid-free remission with inflammatory phenotype [B1 and no perianal disease by the Paris classification].[16] Though this cohort was smaller, results of relapse [33% both groups] and complication rates [20% and 18%] were identical. This suggests that steroid-free remission may be more important for complications and relapse than the actual therapy used to achieve CS-free remission.

The second apparent benefit was for long-term linear growth, as use of CS [even with thiopurines] was associated with a significant decline in height Z scores, whereas EEN was associated with stable height Z scores over time. This benefit was supported by the results of the propensity score analysis which showed better growth in the matched pairs for patients receiving EEN, though the *p*-value just about reached significance [$p = 0.055$]. Our study thus differs from the retrospective study by Grover *et al.*[17] in which follow-up past 1 year demonstrated decreased rates of growth failure for patients in EEN and increased rates of growth failure with CS. This study did not evaluate mean Z scores, and the cutoff for growth failure was set at -1.64 SD. On the other hand, our data support the findings of Cameron *et al.*[9] that early use of EEN did not improve Z scores over 2 years. The significant differences noted in our study are not because of improved growth in the EEN group, rather are due to decreased linear growth in the CS group. It is important to note that we chose to evaluate height Z score and not velocity, since velocity is not a complication whereas decrease in height is a complication. We did not register parental height during the study, so we could not correct for mid parental height. Our study reinforces the concept that other therapies, such as EEN or biologics, might be preferable in children with faltering growth.

Based on meta-analysis, Cochrane reviews, and recent clinical studies,[5,6,11,12] current ECCO guidelines now recommend EEN as the recommended first-line therapy for uncomplicated luminal mild to moderate disease in children, based on equivalent remission and

Table 3. Patients in remission from EEN or CS

	EEN [n = 29]	CS [n = 29]	TOTAL [n = 58]	P value
Age [years]	12.16 ± 2.6	13.16 ± 2.9	12.65 ± 2.7	0.172
Gender [male]	20 [70%]	20 [70%]	40 [70 %]	na
PCDAI Week 0 [median] [IQR]	25 [10–37.5]	30 [10–37.5]	27.5 [20–35]	0.044
CRP Week 0 [mg/dl] [median][IQR]	2.18 [0.66–4.62]	1.1 [0.55–4]	1.96 [0.6–4.34]	0.463
Calprotectin [µg/g] [median][IQR]	1065 [274–1850]	1235 [515–1800]	1235 [290–1800]	0.84
IMM	18 [62.1%]	26 [89.7%]	44 [75.9%]	0.014
Mesalamine without IMM	7 [24.1%]	3 [10.3%]	10 [17.2%]	0.164
Location				
L1	11 [38%]	7 [24%]	18 [31%]	0.209
L2	1 [3%]	4 [14%]	5 [9%]	
L3	19 [66%]	24 [83%]	43 [74%]	
L4a	10 [34%]	18 [62%]	28 [48%]	0.125
L4b	6 [21%]	2 [7%]	8 [14%]	
L4a+L4b	3 [10%]	2 [7%]	5 [9%]	

EEN, exclusive enteral nutrition; CS, corticosteroids; PCDAI, Paediatric Crohn's Activity Disease Index; IQR, interquartile range; CRP, C-reactive protein; IMM, immunomodulators; na, not available.

superior mucosal healing.[1] We believe that our study is the first to validate these recommendations, based on data other than mucosal healing or safety, and the first to demonstrate superiority for remission prospectively. Our data support this recommendation, since better growth and remission rates without compromising risk for complications is consistent with the preference for EEN over CS as the initial recommended therapy.

The GROWTH CD study enrolled consecutive treatment-naïve patients at diagnosis and was geared to prospectively identify remission, relapse, growth, and early complications within 2 years, which is a time frame that is clinically relevant for decisions at diagnosis regarding initial therapy. Our study has provided more data to suggest that EEN is superior or equivalent to CS, depending on the outcome chosen, using long-term outcomes in a prospective cohort designed for this purpose.

There are limitations to this study, including the fact this was not a randomised controlled trial. Choice of therapy varied between institutions, such that some institutions used more CS for their patients and others used EEN more frequently; this may have led to some bias in outcomes. Detection of complications was driven by patient care, and thus we may have missed silent complications, though this bias is true of previous published studies as well. We could not evaluate biologic therapy as a first choice, since the number of patients treated with this therapy at disease onset was very small.

Previous studies have highlighted advantages of EEN over CS, including linear growth, decreased steroid dependence, and lack of side effects in comparison with CS.[1,17–19] On the other hand, EEN is more difficult for parents and patients, and requires more frequent follow-up, and institutional resources.[20] Our study provides additional prospective data comparing these treatments, to allow paediatricians more evidence for clinical decisions in children with CD.

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Conflict of Interest

AL has received grants, honoraria, or served on advisory boards or safety panels from Abvie, Jannsen, Takeda, Nestle, Megapharm. SH has received a speaker fee and travel support from AbbVie. DT in the past 3 years received consultation fee, research grant, royalties, or honoraria from Janssen, MSD, Pfizer, Hospital for Sick Children, Ferring, MegaPharm, AstraZeneca, Abbvie, Takeda, Rafa, Boehringer Ingelheim, Biogen, Atlantic Health, Shire. GV has served as speaker/advisory board for Abvie, Nestle. AS has participated as a clinical investigator for Aboca and Nestlé, was/is advisory board member for Sucampo, consultant for Aboca and D.M.G. Italy, and speaker for Angelini, Danone, Menarini, Miltè, Valeas. RS has received grants from Jannsen, Megapharm and speaker fees from Abbvie, Jannsen, Teva. PL has received advisory board, travel or speaker fees from Nutricia, Nestle, Abbvie, Hospira. JA has received fees for presentations from Danone, Abbvie, Ferring, Ferrer. AP has received speaker/advisory board fees from AbbVie and Nestlé. RKR has received speaker fees and travel support and participated in medical board meetings with Abbvie, Janssen, Shire, Celltrion, and Nestle.

Author Contributions

AL: initiated, organised, and received the grants for the study and participated in preparation of the manuscript; NCD: organisation and analysis of data, preparation of manuscript; TZ and SBS: data analysis; MS, SH, DT, GV, SK, JM, AS, RS, PL, JA, AP, FN, and RR: recruited patients and provided critical revision of the manuscript; TPG: designed CRFs, queried data, and logged data. Data were re-queried and evaluated by NCD, RSB, and CSS. All authors approved the final version of the manuscript.

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