European Journal of Pediatrics (2020) 179:1925–1934
https://doi.org/10.1007/s00431-020-03753-x

ORIGINAL ARTICLE

Exclusive enteral nutrition effect on the clinical course of pediatric Crohn's disease: a single center experience

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Received: 5 November 2019 / Revised: 15 July 2020 / Accepted: 24 July 2020 / Published online: 30 July 2020

Abstract

The aim of this study was to evaluate the short- and long-term outcomes of exclusive enteral nutrition (EEN) versus corticosteroids (CS) as induction therapy, in a cohort of pediatric patients with Crohn's disease (CD). A retrospective study of patients with CD has been conducted. Clinical characteristics, laboratory parameters, and pediatric Crohn's disease activity index (PCDAI) were evaluated at diagnosis and at different follow-up points. Subjects were divided in EEN-induction group, receiving EEN, and CS-induction group, treated with oral CS. We evaluated 47 patients in the EEN-induction group and 21 patients in the CS-induction group. After 8 weeks from diagnosis, we detected a significant improvement in CRP ($p = 0.001$) and albumin ($p = 0.05$), in EEN-induction group compared with the CS-induction group. PCDAI was significantly lower in the EEN-induction group versus the CS-induction group after 8 weeks ($p = 0.04$) and 1 year ($p = 0.03$) of follow-up. After 2 years from diagnosis, the number of subjects needing immunomodulators (IMM, azathioprine or methotrexate) was significantly higher in the CS-induction group compared with the EEN-induction group ($p = 0.02$).

Conclusion: EEN has the same effectiveness of CS therapy in induction of remission but seems to have a more pronounced effect on disease activity. In our cohort, the need to use IMM seems to be reduced in subjects initially treated with EEN.

What is Known:
- *Exclusive enteral nutrition (EEN) has the same effectiveness of corticosteroids (CS) in the induction of remission in pediatric Crohn's disease.*
- *EEN offers numerous advantages over CS, in terms of improved nutrition and mucosal healing.*

What is New:
- *Induction of remission with EEN seems to have a more pronounced effect on disease activity compared to induction with CS.*
- *In our cohort, induction of remission with EEN seems to reduce the need of therapy with immunomodulators at 2 years of follow-up.*

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Communicated by Peter de Winter

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Keywords Inflammatory bowel disease · Nutritional therapy · Natural history · Corticosteroids

Abbreviations

AZT	Azathioprine
BMI	Body mass index
CD	Crohn's disease
CS	Corticosteroids
ECCO	European Crohn's and Colitis Organization
EEN	Exclusive enteral nutrition
EIM	Extra-intestinal manifestations
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology and Nutrition
IFX	Infliximab
PCDAI	Pediatric Crohn's Disease Activity Index
IMM	Immunomodulators
MTX	Methotrexate

Introduction

Crohn's disease (CD) is a chronic inflammatory condition that may involve any part of the gastrointestinal tract, typically following a relapsing-remitting course. It may present at any age, but in up to 25% of patients, CD is diagnosed during childhood [1]. In this period of life, CD presents often with a more complicated disease course compared with adult patients. The cumulative risk of progression to complicated CD is similar to adults but, due to the early onset of disease, children are more likely to have undergone surgery by young adulthood [2]. CD has a heavy impact on the patient's nutritional status, with about 90% of patients showing weight loss at diagnosis. Although the etiology of nutritional problems and growth failure is multifactorial, malnutrition owing to inadequate nutrient intake is the primary cause [3–6]. Moreover, the chronic inflammatory state of CD has a remarkable effect on the patient's growth rate. The ultimate benefit of any treatment for CD is the ability to reduce frequency and severity of inflammatory relapses that contribute to long-term cumulative bowel damage, and these are the endpoints against which each treatment must be measured [7, 8]. The consensus guidelines of the European Crohn's and Colitis Organization (ECCO) and of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) suggest to use exclusive enteral nutrition (EEN) for children with inflammatory luminal diseases as a first-line therapy to induce remission, due to its excellent safety profile [7]. Comparable pediatric remission rates have been reported following treatment with either EEN or corticosteroids (CS) [9–11]. The potential benefits of EEN extend beyond nutrition alone and include improved mucosal healing, linear growth, and bone health [12–15]. Although CS are clinically efficacious and associated with improvements on endoscopic assessment, mucosal healing is significantly less frequent if CS are used, compared with EEN [16]. Their use is also associated with undesirable side effects including deleterious effects on growth and bone mineral density. Short-term EEN efficacy has been clearly demonstrated; however, the relative importance of initial choice for the induction therapy on medium- to long-term outcomes was not as well studied. The aims of our study were to evaluate the short- and long-term clinical effects of EEN versus CS in our cohort of children with CD.

Methods

Population

Our study population included all the subjects aged less than 18 years who received a diagnosis of CD between January 2003 and December 2013 and who were followed up at the Endoscopy and Motility Unit of the Department of Pediatrics, University of Naples "Federico II." Subjects with complex perianal fistulas were excluded from the analysis. The included patients were divided in 2 groups according to the different induction therapy received at CD diagnosis: EEN-induction group, consisting of patients who received EEN, and CS-induction group, consisting of patients treated with oral CS.

Data collection

The demographic and clinical data of each patient were retrospectively collected from medical records, at diagnosis and at different follow-up times (8 weeks, T1; 6 months, T2; 1 year, T3; 2 years, T4). Disease activity was scored using the Pediatric Crohn's Disease Activity Index (PCDAI) [17]. Disease activity was defined as "mild" or "moderate to severe" in the case of PCDAI scores < 30 or > 30, respectively. Remission was defined after the physician's global assessment as a PCDAI score ≤ 10, in the absence of clinical symptoms. Clinical relapse was defined as the occurrence or worsening of symptoms accompanied by a PCDAI score > 10 points, in a subject who had already reached clinical remission. CD was classified according to Paris classification [18]. Extra-intestinal manifestations (EIM) included eye, joint, skin, or liver involvement and persistent fever.

Weight, height, and body mass index (BMI) were collected at diagnosis and at the different time points. Growth velocity was calculated at each visit from two consecutive height measurements performed within an interval of at least 6 months. In order to compare parameters from subjects with different age

and gender, weight, height, BMI, and growth velocity z-scores were calculated considering the general Italian population as a reference. Growth failure was defined as a height for age z-score lower than − 1.64; obesity was defined as a BMI z-score higher than 2. The fasting laboratory parameters (including Hb, ESR, CRP, albumin, and fecal calprotectin) were collected at diagnosis and at the different time points.

Therapeutic approach

Therapeutic decisions, at baseline and follow-up, were made by two expert pediatric gastroenterologists (AS and EM), in line with the validated international guidelines [19]. We included in the analysis our cohort followed before the publication of the 2014 ECCO-ESPGHAN pediatric guidelines with CD risk stratification [7] and prior to biologics' optimization. Therefore, the first therapeutic choice was always represented by EEN (polymeric formula for 6–8 weeks, followed by a gradual introduction of foods during the subsequent 4 weeks). Partial EN was not continued at the end of the induction. CS therapy (oral methylprednisolone: 1 mg/kg/day, max 40 mg/day per 4 weeks, followed by gradual tapering off by week 11) was used in patients who refused EEN or in those patients where EEN was considered not sufficient to induce disease remission, according to the physician's discretion. Children who could not wean steroids after week 12 were defined as steroid-dependent. After the induction, all patients that reached clinical remission started a maintenance therapy with aminosalicylates (5-ASA; mesalazine 50 mg/kg/day, max 4 g/day) or IMM therapy at a standardized dose (azathioprine (AZA), 2–2.5 mg/kg/day; or methotrexate (MTX), 15 mg/m^2/week), according to the physician's discretion. Patients in whom induction therapy had failed, or patients with clinical relapse, were treated with a second cycle of CS or EEN as induction therapy and started IMM as a maintenance therapy. Early use of IMM was defined as use within the first 8 weeks of disease. Biologics were started as a second-line therapy after IMM failure.

Statistical analysis

Variables were screened for their distribution, and appropriate parametric or non-parametric tests were adopted as necessary. Continuous variables were expressed by mean and standard deviation. Qualitative variables were expressed by frequency and percentage. The Student's t test and the Mann-Whitney test for continuous variables and the χ^2 and Fisher's exact tests for categorical variables were used, where appropriate. Statistical significance was predetermined as $p < 0.05$. SPSS version 20 was used for all statistical analyses (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

We included 68 children with CD who received either EEN (n = 47) or CS (n = 21) as the sole induction therapy at diagnosis. Clinical characteristics of the study population at baseline are summarized in Table 1. At diagnosis, there were no significant differences in age, gender, disease's location, and behavior between the two groups. The only exception was represented by EIMs that were significantly more frequent in subjects from the CS-induction group (10/47, 21%, in the EEN-induction group versus 11/21, 52%, in the CS-induction group; p = 0.02). In addition, no significant difference was found in disease activity according to PCDAI (median PCDAI 26.2, range 10–45, and median 32.5, range 10–60, in the EEN-induction group and CS-induction group, respectively; p = 0.13), with 31/47 (66%) in the EEN-induction group and 10/21 (48%) in the CS-induction group showing a "mild" disease and 16/47 (34%) in the EEN-induction group

Table 1 Baseline clinical characteristics of 68 CD pediatric patients, according to the Paris classification (17)

	EEN-induction (N = 47)	CS-induction (N = 21)	p*
Gender			
Male (%)	27 (57)	12 (54.5)	ns
EIM (%)	10 (21)	11 (52)	**0.02**
Disease activity			
PCDAI; median (range)	26.2 (10–45)	32.5 (10–60)	ns
Mild (PCDAI < 30)	31 (66)	10 (48)	ns
Moderate to severe (PCDAI > 30)	16 (34)	11 (52)	ns
Age at diagnosis			
Months; median (range)	129 (37–212)	158 (47–205)	ns
A1a	13 (28)	4 (19)	ns
A1b	34 (72)	17 (81)	ns
Disease location			
L1 (%)	9 (19)	2 (10)	ns
L2 (%)	10 (21)	8 (38)	ns
L3 (%)	28 (60)	11 (52)	ns
Disease behavior			
B1(%)	33 (70)	14 (67)	ns
B2 (%)	14 (30)	7 (33)	ns
P (%)	7 (15)	7 (33)	ns
Growth			
G0 (%)	44 (94)	17 (81)	ns
G1 (%)	3 (6)	4 (19)	ns

CD Crohn's disease, *EEN* exclusive enteral nutrition, *CS* corticosteroids, *EIM* extra-intestinal manifestations

*Fisher's exact test

and 11/21 (52%) in the CS-induction group showing a "moderate to severe" disease ($p = 0.18$). Finally, no statistically significant differences were found in anthropometric and laboratory parameters between the two groups (Tables 2 and 3).

T1 outcomes

At 8 weeks from diagnosis, 32/47 (68%) in the EEN-induction group and 10/21 (48%) in the CS-induction group achieved clinical remission ($p = 0.17$). Eight out of 47 (17%) from EEN-induction group versus 5/21 (24%) from CS-induction group did not respond to induction ($p = 1$). One out of 21 (5%) patients from the CS-induction group presented steroid dependence and could not stop steroid therapy at the end of the induction. In the EEN-induction group, 8/47 (17%) needed a course of CS therapy because of a failure of induction with EEN. The number of subjects who needed an early use of IMM was 6/47 (13%) in the EEN-induction group and 5/21 (24%) in the CS-induction group ($p = 0.29$). In the EEN-induction group compared with the CS-induction group, we detected a significant improvement in CRP values (median 0.3, range 0.3–4.6, and median 0.7, range 0.3–51, respectively; $p = 0.001$), albumin values (median 4.5, range 3.4–5.2, and median 4.3, range 3.6–4.9, respectively; $p = 0.05$), and PCDAI values (median 10, range 0–30, and median 15, range 0–45, respectively; $p = 0.04$). Moreover, we found a trend toward statistical significance for ERS values (median 9, range 1–57, and median 14.5, range 2–35, respectively, $p = 0.06$). The number of subjects with CRP values < 5 mg/dL was significantly lower in the EEN-induction group (47/47, 100%) compared with the CS-induction group (18/21, 86%; $p = 0.03$), while there were no significant differences in the number of subjects with normal albumin, normal calprotectin, and PCDAI score ≤ 10. In addition, we found that the difference in Hb values between T1 and T0 was significantly higher in the EEN-induction group compared with the CS-induction group (median 1.2, range − 2.9–3.5, and median − 0.2, range − 6.2–4.3, respectively; $p = 0.048$). All data on laboratory parameters are summarized in Table 2. No differences in anthropometric parameters were found (Table 3).

T2 outcomes

After 6 months from diagnosis, 39/47 (83%) in the EEN-induction group and 13/21 (62%) in the CS-induction group were in remission ($p = 0.07$). Twelve out of 47 (25.5%) subjects from the EEN-induction group and 7/21 (33%) subjects from the CS-induction group had at least 1 relapse ($p = 0.56$). Two out of 47 (4%) from the EEN-induction group and 1/21 (5%) from the CS-induction group had to perform a course of CS therapy ($p = 1$). Two out of 47 (4%) in the EEN-induction group and 1/21 (5%) in the CS-induction group introduced IMM therapy ($p = 1$). In addition, 1/47 (2%) from the EEN-induction group and 0/21 (0%) from the CS-induction group were on therapy with IFX ($p = 1$). The number of subjects needing the introduction of IMM therapy after 6 months from diagnosis was 8/47 (17%) in the EEN-induction group compared with 6/21 in the CS-induction group (29%), without significant differences between the two groups ($p = 0.33$). As described in Table 2, we found no differences in PCDAI median values and laboratory parameters, with the only exception of the difference in Hb values between T2 and T0, which was significantly higher in the EEN-induction group compared with the CS-induction group (median 1.7, range − 1.7–4.4, and median 0.4, range − 5.4–6.9, respectively; $p = 0.03$). No differences in anthropometric parameters were found (Table 3).

T3 outcomes

At 1 year of follow-up, the number of subjects included in the EEN-induction group was 46, since 1 patient was transferred to the adult care center. Similarly, the subjects evaluated in the CS-induction group were 20 because 1 patient was lost to follow-up (Fig. 1). Thirty-five out of 46 (76%) in the EEN-induction group versus 11/20 (55%) in the CS-induction group were in clinical remission ($p = 0.14$), with 19/46 (41%) subjects from the EEN-induction group and 13/20 (65%) subjects from the CS-induction group that had experienced at least 1 relapse ($p = 0.10$). Moreover, because of a clinical relapse, 3/46 (6.5%) from the EEN-induction group and 1/20 (5%) from the CS-induction group needed to perform a course of CS therapy ($p = 1$), 9/46 (19.5%) from the EEN-induction group and 6/20 (30%) from the CS-induction group started IMM therapy ($p = 0.35$), and 1/46 (2%) from the EEN-induction group versus 2/20 (10%) from the CS-induction group started IFX ($p = 0.21$). So, after 1 year of follow-up, 17/46 (37%) from the EEN-induction group and 12/20 (60%) from the CS-induction group had started a therapy with AZT or MTX ($p = 0.1$), and 2/46 (4%) in the EEN-induction group versus 2/20 (10%) in the CS-induction group had started IFX, with no significant differences between the groups ($p = 0.58$). Considering disease activity, PCDAI values were significantly lower in the EEN-induction group compared with the CS-induction group (median PCDAI 3.75, range 0–40, and median 10, range 0–40, respectively; $p = 0.03$). The difference in Hb values between T3 and T0 was confirmed to be significantly higher in the EEN-induction group compared with the CS-induction group (median 2, range − 0.7–5, and median 1.3, range − 5.2–5.3, respectively; $p = 0.03$). No differences in other laboratory parameters (Table 2) and in anthropometric parameters (Table 3) were found.

Table 2 Laboratory parameters and disease activity at all time points; median (range)

	T0			T1			T2			T3			T4		
	EEN-induction (47)	CS-induction (21)	*p**	EEN-induction (47)	CS-induction (21)	*p**	EEN-induction (47)	CS-induction (21)	*p**	EEN-induction (46)	CS-induction (20)	*p**	EEN-induction (37)	CS-induction (19)	*p**
PCDAI	26.2 (10–45)	32.5 (10–60)	ns	10 (0–30)	15 (0–45)	**0.04**	5 (0–35)	10 (0–30)	ns	3.75 (0–40)	10 (0–40)	**0.03**	5 (0–30)	7.5 (0–35)	ns
- PCDAI ≤ 10	2 (4)	1 (5)	ns	32 (68%)	10 (48%)	ns	39 (83%)	13 (62%)	ns	35 (76%)	11 (55%)	ns	31 (84%)	10 (53%)	**0.02**
- Δ PCDAI TX-T0 °	-	-	-	− 19 (− 42.5–2.5)	− 16.2 (− 45–15)	ns	20 (−5–45)	22.5 (2.5–42.5)	ns	20 (−10–42.5)	17.5 (−20–35)	ns	22.5 (− 5–38)	22.5 (− 25–40)	ns
Hb; g/dL	10.2 (8–14)	11.7 (7–18)	ns	11.5 (9.2–15.2)	11.3 (7.9–15.2)	ns	12.1 (9–15.9)	11.6 (7.6–14.1)	ns	12.5 (9.4–16.3)	12.7 (8.5–15.7)	ns	12.7 (7.3–17.2)	12.5 (9.8–15.8)	ns
- Δ Hb TX-T0 °	-	-	-	1.2 (− 2.9–3.5)	− 0.2 (− 6.2–4.3)	**0.048**	1.7 (−1.7–4.4)	0.4 (− 5.4–6.9)	**0.003**	2 (− 0.7–5)	1.3 (− 5.2–5.3)	**0.038**	2.5 (− 8.8–5)	1.3 (− 5.3–6.2)	**0.002**
ESR; mm	28.5 (2–111)	26 (3–77)	ns	9 (1–57)	14.5 (2–35)	ns	9 (2–70)	6 (2–38)	ns	10 (2–50)	10 (2–40)	ns	5 (2–30)	8 (2–29)	ns
- Δ ESR TX-T0 °	-	-	-	− 20 (− 96–14.6)	− 17.5 (− 69–18)	ns	19 (− 29.6–74)	12 (− 28–73)	ns	20 (−20–67)	8.38 (− 7–67)	ns	21 (−4–96)	7 (− 14–72)	ns
CRP; mg/dL	4.0 (0.3–146.2)	4.3 (0.3–115)	ns	0.3 (0.3–4.6)	0.7 (0.3–51)	**0.001**	0.3 (0.3–88.7)	0.5 (0.3–4.4)	ns	0.3 (0.2–34.2)	0.45 (0.3–41)	ns	0.3 (0.3–20.9)	0.7 (0.3–20.2)	ns
- CRP < 5	25 (53%)	11 (52%)	ns	47 (100%)	18 (86%)	**0.03**	43 (91%)	21 (100%)	ns	40 (87%)	18 (90%)	ns	34 (92%)	16 (84%)	ns
- Δ CRP TX-T0 °	-	-	ns	− 3.7 (− 145–0.58)	− 3.6 (− 113–47.9)	ns	− 2.9 (− 141–82.1)	− 3.9 (− 114.2–3.9)	ns	− 2.0 (− 94.5–20.5)	− 2.8 (− 114–33.4)	ns	− 2.4 (− 94–20.5)	− 3.0 (− 114.3–6.7)	ns
Calpr; mcg/gr	423 (30–1250)	471.5 (95–770)	ns	291.5 (15–1470)	435 (20–610)	ns	253 (15–680)	343 (15–498)	ns	138 (15–500)	181.5 (15–500)	ns	191.5 (15–500)	208 (15–613)	ns
-Calpr < 100	2/45 (4%)	1/18 (5%)	ns	6/44 (14%)	1/18 (5.5%)	ns	9/39 (23%)	4/17 (23.5%)	ns	16/41 (39%)	4/16 (25%)	ns	12/32 (37.5%)	3/15 (20%)	ns
- Δ Calpr TX-T0 °	-	-	ns	− 115 (− 970–1062)	− 36.5 (− 557–395)	ns	− 115 (− 1075–353)	− 117.5 (− 415–128)	ns	− 192.5 (− 1197–500)	− 145 (− 465–317)	ns	− 198 (−812–300)	− 87 (− 480–405)	ns
Alb; g/dL	3. 5 (2.5–5)	3.6 (2.5–4.4)	ns	4.5 (3.4–5.2)	4.3 (3.6–4.9)	**0.05**	4.5 (3.2–5.6)	4.4 (3.9–5)	ns	4.6 (3.6–5.5)	4.6 (3.6–5.2)	ns	4.6 (3.5–5.6)	4.6 (3.1–5.1)	ns
- Alb > 3.5	28 (59.5%)	13 (62%)	ns	44 (94%)	18 (86%)	**ns**	44 (94%)	21 (100%)	ns	46 (100%)	20 (100%)	ns	37 (100%)	16 (84%)	**0.03**
- Δ Alb TX-T0 °	-	-	ns	0.95 (− 3.5–1.9)	0.3 (− 3.7–2)	ns	0.95 (− 0.6–2.1)	0.95 (− 0.1–2.1)	ns	1.05 (− 0.8–2.3)	0.9 (−0.2–2.4)	ns	1 (− 3.7–2.1)	1.05 (− 0.8–2.5)	ns

*Mann-Whitney test; *SD* standard deviation, *EEN* exclusive enteral nutrition, *CS* corticosteroids, *PCDAI* pediatric Crohn's disease activity index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *Calpr* calprotectin, *Alb* albumin

°Δ value TX-T0 defines the median (range) difference in PCDAI/Hb/ESR/CRP/calprotectin/albumin between each time point and T0 (Tx-T0)

Table 3 Anthropometric parameters at all time points

	T0			T1			T2			T3			T4		
	EEN (47)	CS (21)	p*	EEN (47)	CS (21)	p*	EEN (47)	CS (21)	p*	EEN (46)	CS (20)	p*	EEN (37)	CS (19)	p*
Height z-score Median (range)	−0.2 (−2.1–1.5)	−0.7 (−2.9–1.6)	ns	−0.2 (−2–2)	−0.7 (−3.1–1.7)	ns	−0.1 (−2.4–2.2)	−0.35 (−2.7–0.9)	ns	−0.2 (−2.3–2.1)	−0.3 (−2.6–2.7)	ns	−0.2 (−1.9–1.8)	−0.6 (−3–1.2)	ns
Weight z-score Median (range)	−0.9 (−3.3–3)	−1.2 (−4.2–1.4)	ns	−0.3 (−2.9–3)	−0.6 (−2.3–1.9)	ns	−0.3 (−2.2–3.1)	−0.5 (−2.6–1.7)	ns	−0.4 (−2.4–3)	−0.5 (−2.4–2.2)	ns	0.1 (−2.4–2)	−0.5 (−2–1.2)	ns
BMI z-score Median (range)	−1.2 (−4–2)	−0.8 (−5–1)	ns	−0.3 (−3.1–2.4)	−0.1 (−1.5–1.4)	ns	−0.4 (−2.6–2.3)	−0.33 (−1.9–1.5)	ns	−0.2 (−3.9–2.3)	−0.2 (−1.8–1.9)	ns	−0.02 (−2.8–1.9)	0.06 (−2–1.7)	ns
Growth failure n (%)	11 (23.4)	6 (27.3)	ns	3 (6.4)	0 (0)	ns	3 (6.4)	1 (4.5)	ns	4 (8.7)	1 (5)	ns	3 (8.1)	3 (15.8)	ns
Normal growth n (%)	35 (74.5)	16 (72.7)	ns	43 (91.5)	22 (100)	ns	43 (91.5)	21 (95.5)	ns	41 (89.1)	19 (95)	ns	34 (91.9)	16 (84.2)	ns
Normal GV n (%)	-	-	-	-	-	-	28 (59.6)	17 (77.3)	ns	29 (63)	15 (75)	ns	21 (56.7)	13 (68.4)	ns
Obese n (%)	1 (2.1)	0 (0)	ns	1 (2.1)	0 (0)	ns	1 (2.1)	0 (0)	ns	1 (2.2)	0 (0)	ns	0 (0)	0 (0)	ns

*Fisher's exact test or Mann-Whitney test were used for categorical and continues variables, respectively; *EEN* exclusive enteral nutrition, *CS* corticosteroids, *BMI* body mass index, *GV* growth velocity

T4 outcomes

At 2 years of follow-up, the number of subjects included in the EEN-induction group was 37, because 1 patient was transferred to the adult care center and 8 patients were lost to follow-up. The subjects evaluated in the CS-induction group were 19 since 1 patient was transferred to the adult care center. Patient flow through the study is described in Fig. 1. The number of subjects who experienced at least one relapse was not significantly different between the two groups, with 21/37 (57%) in the EEN-induction group versus 15/19 (79%) in the CS-induction group ($p = 0.14$). However, we found a significant difference in the number of subjects in clinical remission between the two groups, with 31/37 (84%) from the EEN-induction group compared with 10/19 (53%) from the CS-induction group that had a PCDAI score ≤ 10 in the absence of clinical symptoms ($p = 0.02$). One out of 37 (3%) in the EEN-induction group and 1/19 (5%) in the CS-induction group needed a course of CS therapy ($p = 1$), 2/37 (5%) from the EEN-induction group and 4/19 (21%) from the CS-induction group started a therapy with IMM ($p = 0.16$), and 4/37 (11%) in the EEN-induction group and 2/19 (10.5%) in the CS-induction group started a therapy with IFX ($p = 1$). Considering the global need to start IMM therapy, we detected a significant difference between the two groups: with 19/37 (51%) in the EEN-induction group versus 16/19 (84%) in the CS-induction group ($p = 0.02$).

Finally, there was no difference in the number of subjects who needed to start IFX (6/37, 16% and 4/19, 21% in the EEN-induction group and CS-induction group, respectively; $p = 0.71$). Clinical outcomes at all time points for both study groups are summarized in Table 4. Overall, 3/47 (6%) subjects from the EEN-induction group had to stop IMM because of side effects. Specifically 2 subjects had an adverse event to AZT (1 neutropenia and 1 pancreatitis), while 1 subject did not tolerate MTX due to GI symptoms. In the CS-induction group, 2/21 (9.5%) subjects had adverse events that required discontinuation of IMM therapy, with 1 subject showing intolerance only to AZT (pancreatitis), while the other being intolerant to both AZT and MTX (allergic reaction). No difference was found in the rate of adverse events between the groups ($p = 0.64$).

As for disease activity and laboratory parameters, no differences were found in median PCDAI scores and laboratory parameters, between the two groups. However, the number of subjects with PCDAI score ≤ 10 was significantly higher in the EEN-induction group (31/37, 84%) compared with the CS-induction group (10/19, 53%; $p = 0.02$), and significantly more subjects had albumin values > 3.5 g/dL in the EEN-induction group (37/37, 100%) versus CS-induction group (16/19, 84%; $p = 0.03$). The difference in Hb values between T4 and T0 was significantly higher in the EEN-induction group compared with the CS-induction group (median 2.5, range − 8.8–5, and median 1.3, range − 5.3–6.2, respectively; $p = 0.02$). Laboratory

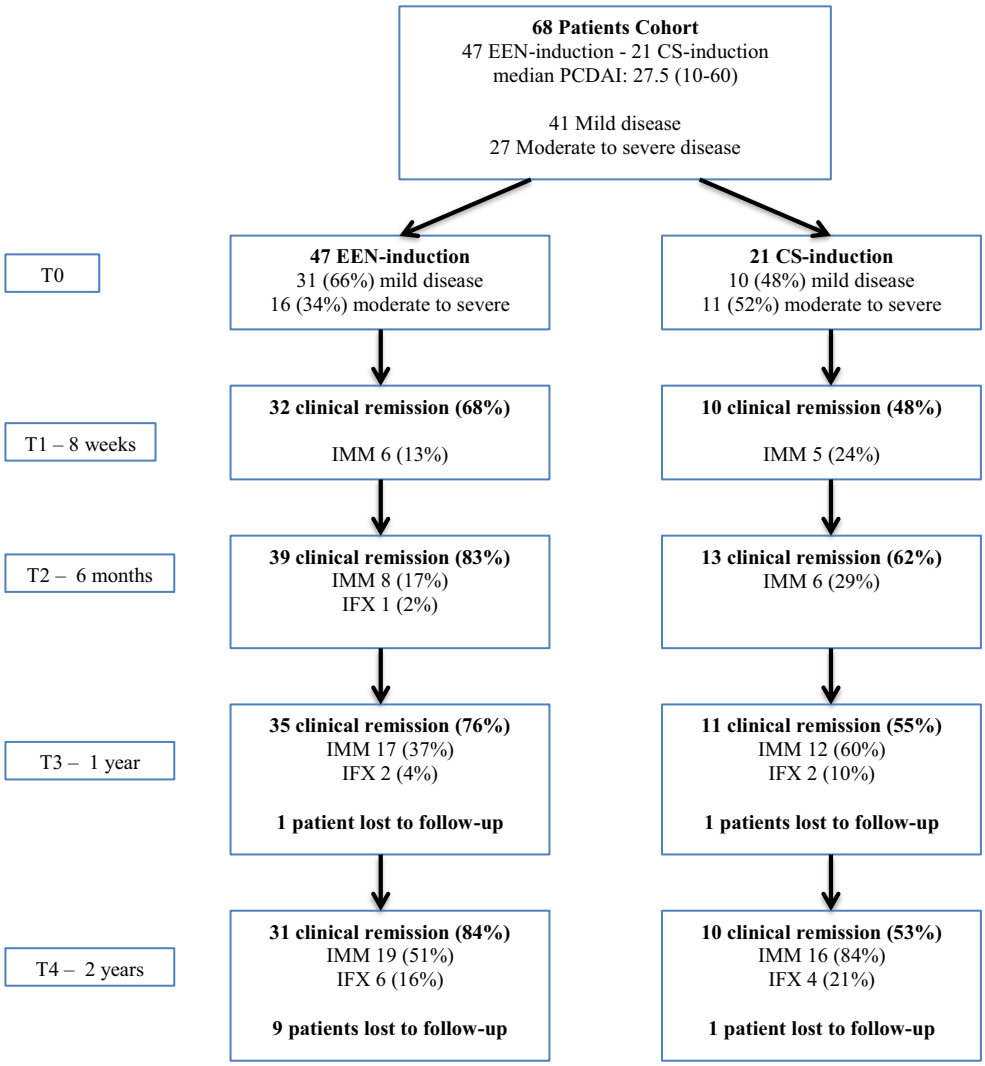

Fig. 1 Patient flow through the study

parameters at all time points are summarized in Table 2. Moreover, no statistically significant differences were found in the anthropometric parameters, between the two groups. However, after 2 years from diagnosis, median BMI z-scores improved from − 1.2 (range 4–2) to − 0.02 (range − 2.8–1.9) in the EEN-induction group ($p < 0.001$) and from − 0.8 (range – 5–1) to 0.06 (range – 2–1.7) in the CS-induction group ($p = 0.03$). Growth parameters at all time points are shown in Table 3.

Discussion

Our data confirm that EEN has the same effectiveness of CS therapy in the induction of clinical remission and suggest a more pronounced effect on disease activity, as demonstrated by the more significant improvement of PCDAI scores at the end of induction and still after 1 year of follow-up in the EEN-induction group compared with the CS-induction

Table 4 Clinical outcomes at all time points

	T1			T2			T3			T4		
	EEN (47)	CS (21)	*p**	EEN (47)	CS (21)	*p**	EEN (46)	CS (20)	*p**	EEN (37)	CS (19)	*p**
At least 1 relapse; n (%)	10 (21)	6 (27)	ns	12 (25.5)	7 (33)	ns	19 (41)	13 (65)	ns	21 (57)	15 (79)	**ns**
AZT or MTX; n (%)	6 (13)	5 (24)	**ns**	8 (17)	6 (29)	ns	17 (37)	12 (60)	ns	19 (51)	16 (84)	**0.02**
IFX n (%)	0 (0)	0 (0)	ns	1 (2)	0 (0)	ns	2 (4)	2 (10)	ns	6 (16)	4 (21)	ns

*Fisher's exact test; *EEN* exclusive enteral nutrition, *CS* corticosteroids, *AZT* azathioprine, *MTX* methotrexate, *IFX* infliximab

group and by the higher number of subjects in clinical remission after 2 years of follow-up, in the EEN-induction group compared with the CS-induction group. Moreover, according to the data from our cohort, induction with EEN seems to reduce the long-term need of IMM therapy. Although we are aware that the retrospective nature of the study may overestimate the benefits of EEN-induction on the need to start IMM, due to the risk of a selection bias, most of our results are in line with the previous published literature. The precise mechanism of action of EEN therapy has not been clearly elucidated. However, according to the available evidence, EEN is more than simple bowel rest, as confirmed by the direct anti-inflammatory effect with regulation of pro-inflammatory cytokine production [20], by the improvement in barrier function and enterocyte differentiation [21, 22], and by the modulation of intestinal microbiota [23]. Previous data showed that clinical response to polymeric diet is associated with a decrease in serum tumor necrosis factor-alpha levels, a downregulation of pro-inflammatory cytokines, and a significant healing of intestinal mucosa [24]. On the contrary, CS have poor ability to modify submucosal inflammatory process [25]. Moreover, it is estimated that nearly half of CD patients who initially respond to CS subsequently develop a dependency on them or have a relapse within 1 year [26]. It is evident that CS do not change the course of CD owing to their inability to affect mucosal lesions of the gut. Our data showed that, 8 weeks after diagnosis, there were no significant differences in the number of patients who achieved clinical remission with EEN compared with those who had used CS. These findings are in agreement with a Cochrane review published in 2018 by Narula et al. [15] that confirmed comparable remission rates between adult and pediatric patients treated with enteral nutrition versus steroids. In particular, the subgroup analysis by age showed that CS were superior to EEN in adults, while enteral nutrition was superior to CS in children. Another recent meta-analysis by Yu et al. [27], including pediatric studies comparing EEN versus CS for the treatment of pediatric CD, confirmed that EEN has the same effectiveness of CS in the achievement of remission. Indeed, numerous studies show that EEN is at least as efficacious as CS therapy in inducing remission and reducing disease activity over the short term for children with CD, but EEN offers numerous advantages in terms of improved nutrition and mucosal healing [28–31].

At the end of induction, we found a significant decrease in PCDAI scores, in patients from EEN group compared with those from the CS group. These findings are in agreement with the meta-analysis from Yu et al. [27] that described a distinct decline of PCDAI in patients who received EEN compared with those who received CS. Also Borrelli et al. [28] found that in children with newly diagnosed CD, a short course of nutritional therapy is as effective as a short course of oral CS in achieving clinical remission, measured with PCDAI. However, nutritional therapy was significantly more effective than CS in healing inflammatory lesions of the gut as documented by endoscopy and histology [12, 32].

Considering nutritional status, after 8 weeks of treatment, the improvement in albumin levels was significantly higher with EEN compared with CS treatment, suggesting a direct effect of EEN on nutritional status. Nevertheless, an improvement in weight for age, height for age, and BMI, both at short- and long-term follow-up, was found without significant difference in both groups, as described also by Yu et al. [27].

Finally, our study compared the long-term effects of the two therapies. At 1 year and 2 years of follow-up, we found no significant differences in the relapse rate between the two groups, in accordance with the meta-analysis from Yu et al. [27] and with data from the study by Cohen-Dolev et al. [29] that followed up newly diagnosed pediatric patients with mild to moderate CD for 2 years in the GROWTH CD study and found no differences in time to relapse or relapse rate in subjects initially treated with EEN compared with those treated with CS.

Furthermore, in our cohort, the use of IMM is less frequent in subjects initially treated with EEN compared with those treated with CS. This result could be related to a protective role of EEN induction therapy in the first years after diagnosis, despite the many variables influencing disease course. Our results are in accordance with the study from Lambert et al. [16], which was the first pediatric study to compare the 2-year outcomes of children treated with EEN to children treated with CS. The authors found that the use of EEN as initial induction therapy determined higher rates of remission, improved growth patterns, lower rates of relapse, and less exposure to CS. Also Berni Canani et al. [33] described positive effects at 12 months in subjects initially treated with EEN compared with subjects who received CS, despite the use of the same maintenance therapy, assuming a role of the more pronounced effect of EEN on mucosal healing.

This study has several limitations including its retrospective nature. Therefore, the two comparative groups were not allocated randomly and we were not able to specifically explore the physician and patient's factors regarding treatment choices and preferences, leading to a potential selection bias. In addition, considering that EIM were more frequent in the CS group compared with the EEN group, it is possible that more severe cases were preferentially treated with CS. This could also partially explain the worst 2-year outcome of subjects initially treated with CS.

Similarly, also the need to start IMM may represent the consequence of a more severe phenotype, rather than a direct benefit of EEN, and therefore we cannot exclude that a selection bias occurred from the starting allocation to the CS-induction group. A larger sample size and longer follow-up

time may have allowed detection of significance in a number of observed trends, especially anthropometric data.

Conclusion

In conclusion, accepting the limitations of our study design, our data confirm the importance of the standard use of EEN as primary therapy in children with newly diagnosed CD, due to the significant amelioration of disease activity and considering the possible reduction in the need of IMM. As well underlined in the most recent meta-analysis, further randomized, controlled studies on defining EEN regimens, influence of dietetic support and protocols on treatment success, and longer-term outcomes are required.

Authors' contributions E.S: Dr. Scarpato conceptualized the study, acquired the data, performed the data analysis, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Scarpato agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

C.S.: Dr. Strisciuglio conceptualized the study, acquired the data, performed the data analysis, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Strisciuglio agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

M. M.: Dr. Martinelli conceptualized the study, performed the data analysis, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Martinelli agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

M. R.: Dr. Russo acquired the data, performed the data analysis, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Russo agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

S. C.: Dr. Cenni acquired the data, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Cenni agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

M. C.: Dr. Casertano acquired the data, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Casertano agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

M. R. S.: Dr. Serra acquired the data, performed the data analysis, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Serra agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A. S.: Dr. Staiano contributed to conception of the study, revised the article critically for important intellectual content, and approved the final manuscript as submitted. Dr. Staiano agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

E. M.: Dr. Miele contributed to conception of the study, revised the article critically for important intellectual content, and approved the final manuscript as submitted. Dr. Miele agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding information There is no funding source.

Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors. The Institutional Review Board of the University of Naples "Federico II" approved the study protocol and questionnaire with the registration number 128/18. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

References

1. Shen YM, Wu JF, Chen LH et al (2011) Characteristics and incidences of pediatric Crohn's disease in decades before and after 2000. Pediatr Neonatol 52:317–320
2. Gasparetto M, Guariso G, Pozza LV et al (2016) Clinical course and outcomes of diagnosing inflammatory bowel disease in children 10 years and under: retrospective cohort study from two tertiary centres in the United Kingdom and in Italy. BMC Gastroenterol 16:35
3. Shamir R, Phillip M, Levine A (2007) Growth retardation in pediatric Crohn's disease: pathogenesis and interventions. Inflamm Bowel Dis 13(5):620–628
4. Walters TD, Griffiths AM (2009) Mechanisms of growth impairment in pediatric Crohn's disease. Nat Rev Gastroenterol Hepatol 6(9):513–523
5. Griffiths AM, Nguyen P, Smith C et al (1993) Growth and clinical course of children with Crohn's disease. Gut 34(7):939–943
6. Ley D, Duhamel A, Behal H, Vasseur F, Sarter H, Michaud L, Gower-Rousseau C, Turck D (2016) Growth pattern in pediatric Crohn's disease is related to inflammatory status. J Pediatr Gastroenterol Nutr 63(6):637–643
7. Ruemmele FM, Veres G, Kolho KL, Griffiths A, Levine A, Escher JC, Amil Dias J, Barabino A, Braegger CP, Bronsky J, Buderus S, Martín-de-Carpi J, de Ridder L, Fagerberg UL, Hugot JP, Kierkus J, Kolacek S, Koletzko S, Lionetti P, Miele E, Navas López VM, Paerregaard A, Russell RK, Serban DE, Shaoul R, van Rheenen P, Veereman G, Weiss B, Wilson D, Dignass A, Eliakim A, Winter H, Turner D, European Crohn's and Colitis Organisation, European Society of Pediatric Gastroenterology, Hepatology and Nutrition (2014) Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. J Crohns Colitis 8(10):1179–1207
8. Perrin JM, Kuhlthau K, Chughtai A et al (2008) Measuring quality of life in pediatric patients with inflammatory bowel disease: psychometric and clinical characteristics. J Pediatr Gastroenterol Nutr 46(2):164–171
9. Whitten KE, Rogers P, Ooi CK, Day AS (2012) International survey of enteral nutrition protocols used in children with Crohn's disease. J Dig Dis 13(2):107–112
10. Heuschkel RB, Menache CC, Megerian JT, Baird AE (2000) Enteral nutrition and corticosteroids in the treatment of acute

Crohn's disease in children. J Pediatr Gastroenterol Nutr 31(1):8–15
11. de Bie C, Kindermann A, Escher J (2013) Use of exclusive enteral nutrition in paediatric Crohn's disease in the Netherlands. J Crohns Colitis 7(4):263–270
12. Grover Z, Burgess C, Muir R, Reilly C, Lewindon PJ (2016) Early mucosal healing with exclusive enteral nutrition is associated with improvement outcomes in newly diagnosed children with luminal Crohn's disease. J Crohns Colitis 10(10):1159–1164
13. Dziechciarz P, Horvath A, Shamir R et al (2007) Meta-analysis: enteral nutrition in active Crohn's disease in children. Aliment Pharmacol Ther 26(6):795–806
14. Day AS, Lopez RN (2015) Exclusive enteral nutrition in children with Crohn's disease. World J Gastroenterol 21(22):6809–6816
15. Narula N, Dhillon A, Zhang D et al (2018) Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev 4:CD000542
16. Lambert B, Lemberg DA, Leach ST, Day AS (2012) Longer-term outcomes of nutritional management of Crohn's disease in children. Dig Dis Sci 57(8):2171–2177
17. Hyams JS, Ferry GD, Mandel FS, Gryboski JD, Kibort PM, Kirschner BS, Griffiths AM, Katz AJ, Grand RJ, Boyle JT, Michener WM, Levy JS, Lesser ML (1991) Development and validation of a pediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr 12(4):439–447
18. Levine A, Griffiths A, Markowitz J, Wilson DC, Turner D, Russell RK, Fell J, Ruemmele FM, Walters T, Sherlock M, Dubinsky M, Hyams JS (2011) Pediatric modification of the Montreal classification for inflammatory bowel disease: The Paris Classification. Inflamm Bowel Dis 17:1314–1321
19. Van Assche G, Dignass A, Reinisch W, van der Woude J et al (2010) The second European evidence-based consensus on the diagnosis and management of Crohn's disease: special situations. J Crohns Colitis 4(1):63–101
20. Greenberg GR, Fleming CR, Jeejeebhoy KN et al (1998) Controlled trial of bowel rest and nutritional support in the management of Crohn's disease. Gut 29(10):1309–1315
21. Budd GR, Aitchison A, Day AS et al (2017) The effects of polymeric formula on enterocyte differentiation. Innate Immun 23(3): 240–248
22. De Jong NS, Leach ST, Day AS (2007) Polymeric formula has direct anti-inflammatory effects on enterocytes in an in vitro model of intestinal inflammation. Dig Dis Sci 52(9):2029–2036
23. Lionetti P, Callegari ML, Ferrari S et al (2005) Enteral nutrition and microflora in pediatric Crohn's disease. J Parenter Enter Nutr 29(4 Suppl):S173–S175 discussion S175-8, S184-8
24. Bannerjee K, Camacho-Hubner C, Babinska K (2004) Anti-inflammatory and growth-stimulating effects precede nutritional restitution during enteral feeding in Crohn disease. J Pediatr Gastroenterol Nutr 38(3):270–275
25. Swaminath A, Feathers A, Ananthakrishnan AN (2017) Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in paediatric Crohn's disease. Alimen Pharmacol Ther 46(7):645–656
26. Tung J, Loftus EV Jr, Freese DK et al (2006) A population-based study of the frequency of corticosteroid resistance and dependence in pediatric patients with Crohn's disease and ulcerative colitis. Inflamm Bowel Dis 12(12):1093–1100
27. Yu Y, Chen KC, Chen J (2019) Exclusive enteral nutrition versus corticosteroids for treatment of pediatric Crohn's disease: a meta-analysis. World J Pediatr 15(1):26–36
28. Borrelli O, Cordischi L, Cirulli M, Paganelli M, Labalestra V, Uccini S, Russo PM, Cucchiara S (2006) Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. Clin Gastroenterol Hepatol 4(6):744–753
29. Cohen-Dolev N, Sladek M, Hussey M et al (2018) 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. J Crohn's Colitis 12(3):306–312
30. Fell JM, Paintin M, Arnaud-Battandier F et al (2000) Mucosal healing and a fall in mucosal pro-inflammatory cytokine m-RNA induced by a specific oral polymeric diet in pediatric Crohn's disease. Aliment Pharmacol Ther 14(3):281–289
31. Newby EA, Sawczenko A, Thomas AG et al (2005) Interventions for growth failure in childhood Crohn's disease. Cochrane Database Syst Rev 3:CD003873
32. Grover Z, Muir R, Lewindon P (2014) Exclusive enteral nutrition induces early clinical, mucosal and transmural remission in pediatric Crohn's disease. J Gastroenterol 49(4):638–645
33. Berni Canani R, Terrin G, Borrelli O, Romano MT, Manguso F, Coruzzo A, D'Armiento F, Romeo EF, Cucchiara S (2006) Short- and long-term therapeutic efficacy of nutritional therapy and corticosteroids in paediatric Crohn's disease. Dig Liver Dis 38:381–387