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ORIGINAL ARTICLE—ALIMENTARY TRACT

Exclusive enteral nutrition induces early clinical, mucosal and transmural remission in paediatric Crohn's disease

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Abstract
Background and aims Exclusive enteral nutrition (EEN) induces clinical and mucosal healing (MH) in Crohn's disease (CD), with MH the best determinant of future outcome. We investigated efficacy of EEN for inducing early clinical, biochemical, mucosal and transmural remission of CD and related early endoscopic response to outcomes at 1 year.
Methods In a prospective, open label study 34 children (mean 13.1 years; 21 males) with new diagnosis CD were offered EEN, 26 completed a minimum 6 weeks EEN and underwent paired clinical, biochemical and endoscopic assessment at start and completion using PCDAI, BMI, CRP and Simple Endoscopic Score for CD (SES-CD). A subset, 16/26, had paired MR enterography scored. Early good endoscopic response (complete MH, or near complete, SES-CD 0–3) was related to outcome at 1 year.
Results EEN improved mean PCDAI (37.88–7.01, $p < 0.001$; BMI Z scores (-1.54 to -0.54, $p < 0.01$); weight Z score (-0.79 to -0.08, $p < 0.03$); CRP (44.86–5.5, $p < 0.001$); endoscopy (SES-CD 14.28–3.88, $p < 0.001$) and MRE (5.14–2.79, $p = 0.01$). Of 26 children, 22 (84 %) achieved clinical remission; 20 (76 %) biochemical remission. Fifteen (58 %) had early good endoscopic response (11 complete, 4 near complete MH) and 3/14 (21 %) had complete transmural remission of ileal CD (MRE-CD: 0–1). Early good endoscopic response was associated with reduced endoscopic confirmed relapse (53 vs. 100 %, $p = 0.02$), anti-TNF use (33 vs. 88 %, $p = 0.01$) and hospitalisation (40 vs. 88 %) at 1 year.
Conclusions EEN is effective for inducing early clinical, biochemical, mucosal and transmural remission. Early endoscopic remission improves outcomes at 1 year.

Keywords Enteral nutrition · Mucosal healing · Paediatric Crohn's disease

Introduction

Crohn's disease (CD) is a chronic, debilitating disorder affecting growth, well-being, education, and employment and nearly 25 % of patients are diagnosed before 16 years of age [1]. Paediatric onset Crohn's disease is a more severe phenotype with the additional issues of growth failure, delayed puberty, poor bone density and the consequences of a chronic disease commencing at a vulnerable period of psychosocial development [2–10]. Cohort studies comparing the clinical course of paediatric versus adult onset CD confirms its more aggressive phenotype with extensive intestinal involvement, rapid progression and increased disease activity index, year by year, despite use of more immunosuppression [11–13]. These observations demonstrate the need for both better treatment endpoints and interventions in the paediatric population. Mucosal healing has emerged as an important end point which,

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when achieved in the first year, leads to less frequent clinical relapses, fewer hospitalisations, reduced surgical resections and lower risk of fistulising disease [14–16].

Treatments for induction of remission in CD include corticosteroids, exclusive enteral nutrition (EEN) and biologic agents. For clinical remission high quality studies and those in paediatric cohorts comparing steroids and EEN show them to be equally effective in up to 80 % of patients [17]. However, clinical remission indicated by improved symptom control alone is inadequate. Not only is mucosal disease active in the majority of asymptomatic patients treated with steroids [18] but treatment to this endpoint over the past 20 years has failed to avert the progressive and complicated course of CD [13], particularly in children. Our hypothesis was that EEN induces good early mucosal healing and achieving this followed by standard practice early introduction of thiopurine (azathioprine or 6-mercaptopurine <3 months) leads to sustained clinical remission and improved clinical outcomes.

Material and methods

Patients and study design

This was a prospective, single centre, open label study including newly diagnosed children with CD (≤16 years) conducted between November 2009 and December 2012 in a tertiary referral paediatric hospital. Institutional ethics approval was granted and written consent obtained from patients and parents. The diagnosis of CD was based on established clinical, endoscopic, histological and radiological criteria. All new diagnoses of CD were offered EEN as the preferred first line therapy. Eight children over the study period elected for steroids as a sole induction therapy and were not eligible for the trial. Other exclusion criteria included: stricturing disease with proximal bowel dilatation and obstructive symptoms; previous exposure to steroids, thiopurines, biological agents; inability to tolerate oral or nasogastric (NG) tube EEN for a minimum of 6 weeks.

All enrolled patients underwent comprehensive assessment including PCDAI, growth parameters, CRP, endoscopy at diagnosis and 8 weeks. Children were offered either Nutrison (1 kcal/ml, Nutricia UK, 40 g protein, 39 g fat/1000 ml) through nasogastric tube (NGT) or resource protein (1.25 kcal/ml, Nestle, 18.8 g protein, 7 g fat/200 ml) orally based on their preference and dietetic consultation. The prescribed volumes were based on Schofield's equation which predicts resting energy expenditure [19]. Feeds were gradually increased to target volumes in 3–5 days. For those electing to receive EEN via NGT, informed consent was obtained for NGT insertion during general anaesthetic for diagnostic endoscopy, if CD was confirmed. Small amounts of clear fluids and jelly were allowed empirically and concurrently to improve palatability and those struggling with oral EEN were allowed to add small amounts of flavouring or change to NG route. To maximise compliance with EEN, clinical and dietetic staff provided support with regular phone calls and outpatient visits. After completion of EEN and during remission phase no dietary restrictions were recommended.

Primary end points of the study were to determine efficacy of EEN for inducing early clinical, biochemical, mucosal and transmural remission at 8 weeks. Secondary outcomes were to relate early endoscopic response to subsequent clinical outcomes, specifically endoscopic confirmed relapse, CD related hospitalisation, need to commence biological agent and surgical resection at 1 year.

It is our practise to commence thiopurines (azathioprine or 6-mercaptopurine) during or shortly after EEN induction therapy based on the Markowitz publication confirming lower clinical relapse in children with early introduction of 6-MP after steroid induction therapy [20]. Time to initiate thiopurines was at the discretion of the treating gastroenterologist. All children were eventually started on thiopurines within 3 months of their initial diagnosis aiming for 2–2.5 mg/kg/day, modified according to TPMT status and drug monitoring, 6-TG levels >250 pmol/8 $\times$ 10^8 erythrocytes. Current Australian Pharmaceutical Benefits Scheme (PBS) criteria in children restrict use of infliximab to those with complex perianal fistulising disease or active clinical/endoscopic disease after a minimum 8 weeks EEN or steroids and 3 months conventional immunomodulator (thiopurines or methotrexate) use. Hence, no patient was eligible for "early" or step down biological therapy.

Two children were excluded from the study after presenting with stricturing ileocaecal disease and obstructive symptoms associated with proximal dilatation on MR enterography and went to surgery. Eight children with stricturing/fistulising disease without obstructive symptoms were offered EEN prior to consideration for surgery with the expectation to improve nutrition and reduce inflammatory load.

Definitions

Phenotype

Classification was based on previously published modified Montreal/Paris classification [21]; presence of growth failure was defined as (Z score −1.64 corresponding to <5th percentile) as G1, and G0 as no growth failure [7]. BMI Z scores were calculated using Center for Disease Control (CDC) growth charts and BMI Z scores <−1, <−2, <−3 defined grades 1, 2 and 3 thinness, respectively, based on proposed international expert guidelines [22].

Disease location was defined using abnormal endoscopic appearance; abnormal histopathology in otherwise normal appearing mucosa was disregarded for the purpose of disease classification [21]. Extensive intestinal involvement was classified as ileocolonic and upper GI (L3 + L4) disease. Small bowel CD out of reach of endoscopy was defined using standard MR enterography criteria; bowel wall thickness >3 mm, contrast transmural enhancement, skip lesions, stricturing/fistulising disease plus other supportive features like fibro-fatty proliferation, mesenteric lymphadenopathy and comb sign [23].

Clinical and biochemical disease activity

Clinical remission was defined as PCDAI < 10; biochemical remission, CRP < 5 mg/l with PCDAI < 10 [24–27]. Relapse was defined as PCDAI > 15 on more than one occasion 1 week apart and or CRP > 5 mg/l with clinically active disease. A PCDAI > 30 was considered moderate to severe paediatric CD [25].

Mucosal disease activity

Scores were determined by the endoscopist at the time of the procedure using the validated Simple Endoscopic Score (SES) for CD [28]: SES-CD 4–10 mild active disease; 11–19 moderate active and >19 severe active CD. Complete mucosal healing was SES-CD 0; near complete SES 1–3; incomplete >3 [29]. Early good endoscopic response was defined as complete or near complete mucosal healing at 8 week follow up endoscopy. Those with partial or no response, SES > 3 were classified as poor endoscopic response.

Transmural disease activity

Previously validated MRI disease activity scores were applied to each MRE by an experienced radiologist, blinded to endoscopy reports, to determine transmural disease activity of small bowel. Small bowel CD activity was defined: 0–1 no activity, 2–6 mild activity, >7 moderate to severe activity [30].

Statistical methods

All statistical calculations were performed using Graph Pad Prism version 5.00 for Windows, Graph Pad Software, San Diego, CA, USA. Descriptive continuous data is reported as an inter-quartile range. Baseline disease characteristics including CD phenotype, behaviour, severity, time to diagnosis and early immunomodulators use were compared between early good and early poor endoscopic responders using both parametric unpaired *T* and nonparametric Mann Whitney *U* test. Primary end points of disease activity scores before and after intervention were calculated using both paired *T* and non parametric Wilcoxon ranked sum test. Secondary outcomes at 1 year and last follow up were analysed by creating 2 × 2 contingency table using Fisher exact test. *p* value <0.05 was used for significance.

Results

Baseline demographic and phenotypic characteristics (Table 1)

Forty-two patients were diagnosed with CD during the study period (8 preferred steroid induction therapy). Thirty-four children were eligible for the trial and 8 excluded: 2 received concurrent anti-TNF agent for fistulising perianal disease; 2 received concurrent steroids: 1 for autoimmune hepatitis and arthritis, 1 for arthritis and erythema nodosum; 2 were unable to complete EEN for 6 weeks because of abdominal pain and diarrhoea and were changed to steroid. No other adverse effects were reported; 2 children went to surgery for obstructive stricturing disease. Twenty-six children completed a minimum 6 weeks EEN, median duration EEN 9 weeks (IQR 6–14). Median duration of symptoms before diagnosis was 4 months (IQR 3–11). All patients had paired clinical, biochemical and endoscopic assessment at baseline and after 8 weeks EEN; and 16/26 had paired MRE. Of 26, 12 completed EEN via oral route alone, 14/26 received EEN via NG tube because of palatability, inadequate intake or poor compliance. Follow up colonoscopy with ileal intubation was successful in all except one where ileal stricture precluded intubation. Baseline disease phenotype of the 26 eligible children was: median age 13.1 years (9.5–15.75 IQR), 19 males; ileocolonic disease in 21 (80 %), stricturing 8 (31 %, which includes 1 penetrating); perianal 4 (15 %). At diagnosis: clinical disease activity was moderate to severe, PCADI > 30 in 23 (88 %); endoscopic disease activity was mod-severe SES-CD > 10 in 22 (84 %); MRE was active in 24 (92 %) children at diagnosis: moderate to severe in 4 (15.4 %); BMI *Z* scores were <−1 in 18 (70 %, grade 1 thinness) and <−2 in 7 (27 %, grade 2–3 thinness). Growth failure (*Z* score <1.64) at diagnosis was observed in 4/26(15 %). Sixteen (62 %) initiated early thiopurines (<8 weeks) at median 4 weeks (IQR 3–8 weeks).

Primary end points at 8 weeks

Significant overall improvement in pre-treatment disease activity was observed in PCDAI, weight, BMI, CRP, SES-CD and small bowel MRI disease activity scores (Table 2). After completion of EEN 22 (84 %) were in clinical

Table 1 Phenotype and clinical characteristics of study children at diagnosis ($N = 26$)

Age (years) median (IQR)	13.10 (9.5–15.75)
Sex (male/female)	19/7
Duration of symptoms before diagnosis	Median 4 months (IQR 3–11)
Distribution (%)	$N = 26$
Age	
A1a (0 to <10)	2 (8)
A1b (10–17)	24 (92)
Disease	
Ileocolonic L3	21 (81)
Ileal L1	4 (15)
Colonic L2	1 (4)
Disease modifier (%)	Upper GI
Upper GI (L4a + L4b)	14 (53)
L4a (proximal to ligament of Treitz)	10 (38)
L4b (distal to treitz)	1 (4)
L4a + L4b (both)	3 (11)
Perianal	4 (15)
Disease behaviour (%)	
Inflammatory (B1)	18 (70)
Stricturing (B2)	7 (27)
Fistulising/stricturing (B2 + B3)	1 (3)
Growth failure (%)	
Growth failure present (G1)	4 (15.4)
No Growth failure (G0)	22 (84.6)
Clinical disease severity PCDAI (%)	
Mild <30	3 (11.5)
Moderate to severe >30	23 (88.5)
Endoscopic disease severity (%)	
Mild (SES-CD 4–10)	4 = 15 %
Moderate (SES-CD 11–19)	16 = 62 %
Severe (SES-CD >19)	6 = 23 %
MRI disease activity	
No activity (0–1)	2 (8)
Mild (2–6)	20 (77)
Moderate to severe (>7)	4 (15)
Timing to endoscopic re-evaluation	
Median weeks from start of EEN(IQR)	8 (7.35–8.8)
Median weeks from starting immunomodulators (IQR)	4 (1–5.95)
Follow up	
Median mo from diagnosis (IQR)	17.85 (11.47–21.83)

remission; 20 (76 %) in both biochemical and clinical remission; 11 (42 %) children had complete mucosal healing (SES = 0); 4 (16 %) near complete healing (SES 1–3) to give an early good endoscopic response rate of 58 %; 8 (30 %) improved but had incomplete healing

Table 2 Clinical, endoscopic and MRI disease activity before and after 8 weeks EEN

Patient characteristics	Before EEN	After EEN	p value
Mean weight Z score	−0.79	−0.08	0.03
Mean height Z score	−0.19	−0.005	NS
Mean BMI Z score	−1.40	−0.54	<0.01
Mean PCDAI	37.88	7.01	<0.001
Mean CRP	44.86	5.5	<0.001
Mean SES-CD	14.28	3.88	<0.001
Mean MRI score	4.69	2.63	0.01

SES > 3; 3 (11 %) had no response (Fig. 1). On further sub-analysis a higher rate of good endoscopic response was seen in Colonic versus Ileal disease segments but did not reach significance (61.5 vs. 53.84 %, $p > 0.05$). MRE showed complete transmural remission of small bowel CD activity in 3/14 (21 %); significant improvement in 9/14 (64 %); no response (15 %) 2/14.

Comparison of baseline disease severity, phenotype and IM use in those with good (SES-CD < 3) versus poor (SES-CD >3) early endoscopic response

PCDAI, BMI, CRP, SES-CD, early introduction of thiopurines (<8 weeks) and disease phenotype were not statistically different in those with good versus poor early endoscopic response. However, there was a nearly significant trend towards better baseline BMI (−0.95 vs. −2.13, $p = 0.06$) and shorter time to diagnosis from the onset of first symptoms (5.33 vs.10.52 weeks, $p = 0.07$) in those with good early endoscopic response (Fig. 2).

Comparison of baseline disease severity and phenotype between early (<8 weeks) versus subsequent thiopurines use (Table 3)

PCDAI, BMI, CRP, SES-CD and disease phenotype were not statistically different in those with early versus subsequent use of thiopurines.

Secondary end points at 1 year ($n = 24$)

Median follow up was 20.54 months (14.16–24.53 IQR). Subsequent clinical outcomes, specifically endoscopic confirmed relapse, hospitalisation directly related to CD, need to commence anti-TNF agent and surgical resection were analysed at 1 year ($n = 24/26$). Early good endoscopic response led to decreased: endoscopic confirmed relapse (53 vs. 100 %, $p = 0.02$), hospitalisation (40 vs. 88 %, $p = 0.03$), need for anti TNF for luminal disease (33 vs. 88 %, $p = 0.01$) and surgical resection (20 vs. 44 %, NS) at 1 year.

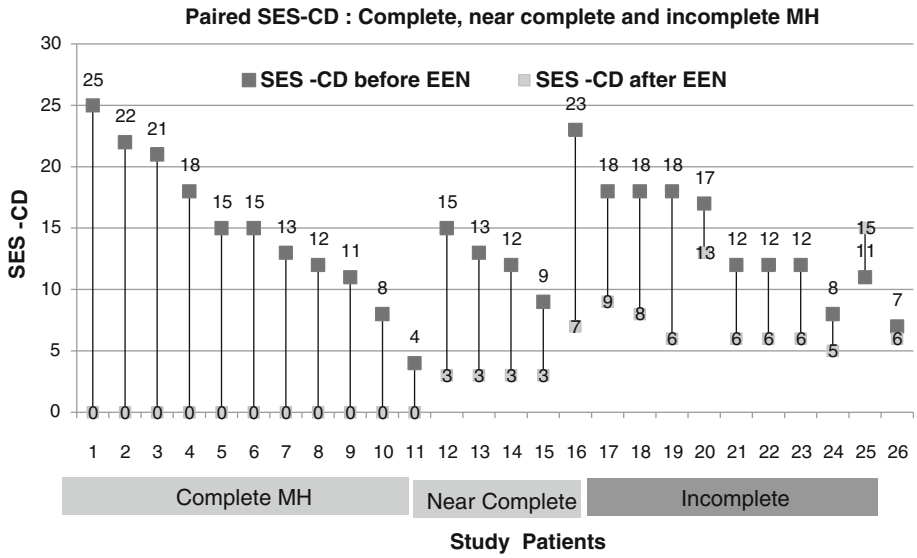

Fig. 1 Paired Simple Endoscopic Score (*SES-CD*) for each patient *before* and *after EEN*

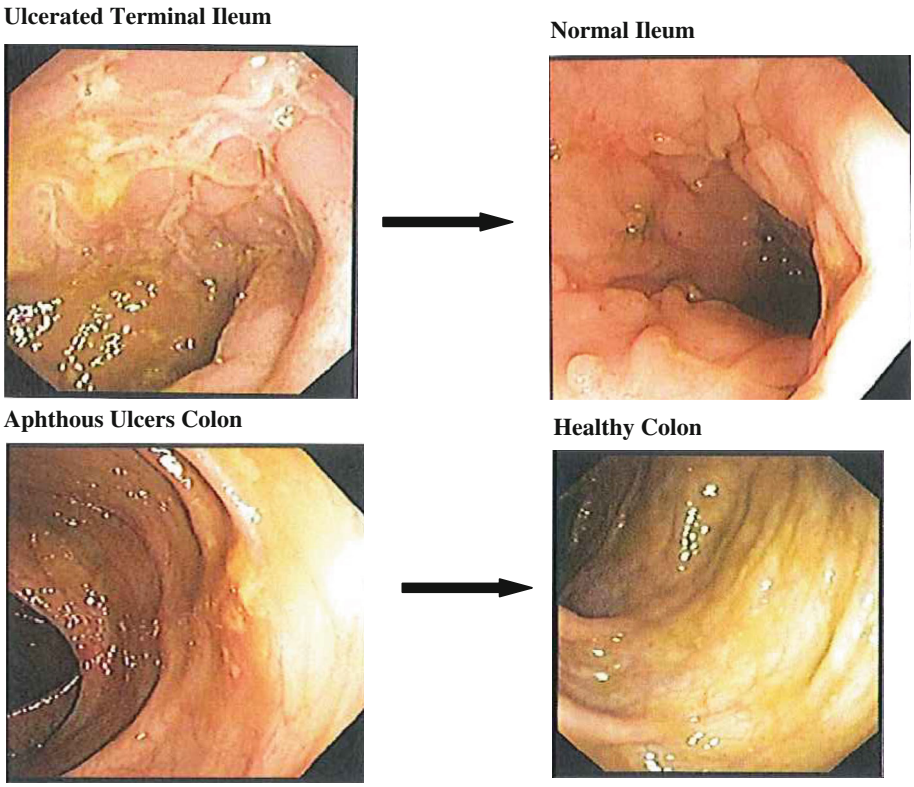

Fig. 2 Typical endoscopic images from a study child demonstrating complete MH after EEN

Also, early thiopurines use (<8 weeks) was not associated with improved outcomes at 1 year (data not shown).

Outcomes of complicated versus inflammatory phenotype

Complicating (stricturing and/or fistulising) versus Inflammatory phenotype at diagnosis was more frequently associated with moderate to severely poor BMI *Z* score <−2.0 in 5/8 versus 3/16 ($p < 0.01$) and longer duration of symptoms before diagnosis (mean 12.15 vs. 5.47 months $p < 0.02$). Seven of 8 of our cohort with non-obstructive stricturing at presentation required surgical resection despite improvement in mucosal disease severity (mean SES 14.38 at diagnosis to mean SES 5.50 post EEN, $p < 0.05$) and BMI recovery (mean *Z* score −1.72 at diagnosis to −0.76, $p > 0.05$). Good endoscopic response was only observed in 3/8 complicating disease, confirming the impression EEN works best for

Table 3 Comparison of CD phenotype at diagnosis between early (<8 weeks) versus subsequent IM (>8 weeks) use

	Early IM (<8 weeks)	Subsequent IM (>8 weeks)	*p* value
Number	16	10	
Mean PCDAI	39.06	36	NS
Mean BMI	−1.5	−1.37	NS
Mean CRP (5 mg/l)	56.19	26.10	NS
Mean SES-CD	15.60	12.30	NS
Ileocolonic disease	13 (81 %)	8 (80 %)	NS
Extensive disease (ileocolonic + UGI)	11 (68 %)	10 (100 %)	NS
Complicating disease	4 (25 %)	4 (40 %)	NS

patients with inflammatory phenotype. Even in stricturing patients, EEN corrected poor nutrition and improved clinical status in preparation for successful surgery.

Discussion

This study is the first to address comprehensively and prospectively the early impact of EEN on clinical, biochemical, endoscopic and MRE parameters in children with moderate to severe CD. EEN gives excellent early clinical response, weight recovery, biochemical remission and mucosal healing. This study is also the first to evaluate the impact of EEN induced early mucosal healing on subsequent medium term outcomes in children receiving maintenance therapy with thiopurines.

EEN is highly effective for the induction of disease remission exceeding most currently reported treatment endpoints, providing complete mucosal healing in over 40 % of children and transmural remission of small bowel CD in 21 %. Previous trials with EEN used variable definitions of mucosal healing but we chose a more rigorous, simpler endpoint, that of complete mucosal healing (complete disappearance of ileocolonic ulceration) to provide compelling evidence of efficacy. We also demonstrated improved transmural disease activity in those with ileal or ileocolonic CD utilising MR enterography in a subset of children.

Our early mucosal healing rates are comparable to other trials of EEN. A single Paediatric RCT in newly diagnosed children with CD comparing EEN versus steroids demonstrated EEN to give endoscopic remission (using CD-EIS) of 74 % at 10 weeks, comparable to our more rigorous definition of good endoscopic response (SES-CD < 3) of 58 % [31]. In treatment naïve adults with CD, EEN gave complete endoscopic remission rate of 44 % at terminal ileum and 39 % in colon at 4 weeks [32]. In contrast, our study showed higher but non-significant good endoscopic response in colonic versus ileal disease segments (61.5 vs. 53.8 %, $p > 0.05$). Both studies were underpowered to discriminate a difference but consistent with a recent study and systematic analysis which concluded disease phenotype does not influence EEN induced clinical remission rates [33, 34].

These well characterized outcomes, specifically early mucosal healing, compare favourably with all currently available induction therapies, including anti-TNF agents and particularly superior to steroids. Steroids have poor ability to induce mucosal healing with active endoscopic disease in 71 % despite clinical remission, with only 12 % achieving complete mucosal healing [18]. An endoscopic substudy of ACCENT 1 using scheduled infliximab therapy in a comparable adult cohort of treatment naïve CD patients reported 29 % complete mucosal healing at 10 weeks [35]. Our study demonstrated better endoscopic response with more complete mucosal healing and greater drop in mean SES-CD (14.28–3.8, $p < 0.001$).

Our study was not designed to address the impact of early thiopurine (<8 weeks) use on early mucosal healing or subsequent clinical outcomes. Most children commenced thiopurines after 4 weeks of EEN to optimise patient vaccination status and the delayed peak efficacy meant use or otherwise was unlikely to affect clinical, biochemical and endoscopic outcomes less than 4 weeks later. There are no published studies looking at mucosal healing before 16 weeks of immunomodulator treatment [36–39].

Our small cohort presented with a high proportion of complicated phenotypes (8/26, 31 %) and this is reflected in the high rate of adverse longer term outcomes despite excellent early clinical response. At 1 year, 17/24 (71 %) had relapsed, 13/24 (54 %) commenced anti-TNF, 14/24 (58 %) had been hospitalised and 7/24 (29 %) had surgical resection. A recent French paediatric cohort study reported complicating disease rates of 28 % at presentation with cumulative probability of surgical resection 31 % at 10 years and 54 % at 20 years from diagnosis, respectively [40]. Seven of 8 of our cohort with non-obstructive stricturing at presentation required later surgical resection despite improvement in mucosal disease severity in 50 %, confirming EEN works best for patients with inflammatory phenotype. Even in stricturing patients, EEN corrected poor nutrition and improved clinical status in preparation for successful surgery.

We confirmed superior outcomes at 1 year in those with early good endoscopic response with reduced; endoscopic confirmed clinical relapses (53 vs. 100 %, $p = 0.02$), hospitalisation (40 vs. 88 %, $p = 0.03$); and need for anti-TNF for luminal disease (33 vs. 88 %, $p = 0.01$). We found no difference in outcomes between those receiving early (<8 weeks) versus later commencement of thiopurines.

Our finding that early mucosal healing from EEN may be more important than early introduction of thiopurines for improving subsequent clinical outcomes has support. In a placebo controlled RCT with adalimumab in adults with moderate to severe CD the importance of early mucosal healing was demonstrated with a positive of predictive effect of early (12 weeks) mucosal healing on CDAI at 52 weeks [41]. Earlier azathioprine therapy versus later, "on demand" azathioprine were not associated with better outcomes in adults with disabling CD. Specifically; clinical remission rate (61 vs. 50 %), anti-TNF use (29 vs. 26 %) and surgery (11 vs. 21 %, $p = 0.11$) [42].

Our cohort of newly diagnosed children with CD has high frequency of anti-TNF agent use (15/26, 58 %); however, this reflects the changing practice of paediatric Crohn's with new treatment endpoints, endoscopic remission and avoidance of steroids aiming for optimal future outcomes. Nevertheless, those with early good mucosal response have reduced anti-TNF use at 1 year. Our study also highlights poor outcomes in those not achieving early mucosal healing providing a strong case for earlier consideration of anti-TNF therapy.

In conclusion, CD in children is recognised as a more aggressive phenotype than in adults and needs improved treatment endpoints. We demonstrate EEN to be highly effective for inducing early endoscopic and transmural healing in treatment naive children with moderate to severe CD. Early mucosal healing with EEN and thiopurines does not prevent most children with stricturing disease coming to surgery, but reduces rates of endoscopic confirmed relapse, hospitalisation and introduction of anti-TNF agents at 1 year.

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

References

1. Goodhand J, Dawson R, Hefferon M, et al. Inflammatory bowel disease in young people: the case for transitional clinics. Inflamm Bowel Dis. 2010;16:947–52.
2. Kanof ME, Lake AM, Bayless TM. Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. Gastroenterology. 1988;95:1523–7.
3. Motil KJ, Grand RJ, Davis-Kraft L, et al. Growth failure in children with inflammatory bowel disease: a prospective study. Gastroenterology. 1993;105:681–91.
4. Sawczenko A, Ballinger AB, Savage MO, et al. Clinical features affecting final adult height in patients with pediatric-onset Crohn's disease. Pediatrics. 2006;118:124–9.
5. Hildebrand H, Karlberg J, Kristiansson B. Longitudinal growth in children and adolescents with inflammatory bowel disease. J Pediatr Gastroenterol Nutr. 1994;18:165–73.
6. Alemzadeh N, Rekers-Mombarg LT, Mearin ML, et al. Adult height in patients with early onset of Crohn's disease. Gut. 2002;51:26–9.
7. Lee J, Escher J, Shuman M, et al. Final adult height of children with inflammatory bowel disease is predicted by parental Height and patient minimum height *Z* score. Inflamm Bowel Dis. 2010;16:1669–77.
8. Burnham JM, Shults J, Semeao E, et al. Body-composition alterations consistent with cachexia in children and young adults with Crohn disease. Am J Clin Nutr. 2005;82:413–20.
9. Schoon EJ, Blok BM, Geerling BJ, et al. Bone mineral density in patients with recently diagnosed inflammatory bowel disease. Gastroenterology. 2000;119:1203–8.
10. Walther F, Fusch C, Radke M, et al. Osteoporosis in pediatric patients suffering from chronic inflammatory bowel disease with and without steroid treatment. J Pediatr Gastroenterol Nutr. 2006;43:42–51.
11. Vernier-Massouille G, Balde M, Salleron J, et al. Natural history of pediatric Crohn's disease: a population-based cohort study. Gastroenterology. 2008;135:1106–13.
12. Van Limbergen J, Russell RK, Drummond HE, et al. Definition of phenotypic characteristics of childhood-onset inflammatory bowel disease. Gastroenterology. 2008;135:1114–22.
13. Pigneur B, Seksik P, Viola S, et al. Natural history of Crohn's disease: comparison between childhood- and adult-onset disease. Inflamm Bowel Dis. 2010;16:953–61.
14. D'Haens G, Baert F, van Assche G, et al. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. Lancet. 2008;371:660–7.
15. Baert F, Moortgat L, Van Assche G, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. Gastroenterology. 2010;138:463–8.
16. Schnitzler F, Fidder H, Ferrante M, et al. Mucosal healing predicts long-term outcome of maintenance therapy with infliximab in Crohn's disease. Inflamm Bowel Dis. 2009;15:1295–301.
17. Dziechciarz P, Horvath A, Shamir R, et al. Meta-analysis: enteral nutrition in active Crohn's disease in Children. Aliment Pharmacol Ther. 2007;26:795–806.
18. Modigliani R, Mary JY, Simon JF, et al. Clinical, biological and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Thérapeutique des Affections Inflammatoires Digestives. Gastroenetrology.1990;98:811–8.
19. Hill R, Lewindon P, Withers G, et al. Ability of commonly used prediction equations to predict resting energy expenditure in children with inflammatory bowel disease. Inflamm Bowel Dis. 2011;17:1587–93.
20. Markowitz J, Grancher K, Kohn N, et al. A multicenter trial of 6-mercaptopurine and prednisone in children with newly diagnosed Crohn's disease. Gastroenetrology. 2000;119:895–902.
21. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis. 2011;17:1314–21.
22. Cole TJ, Flegal KM, Nicholls D, et al. Body mass index cut offs to define thinness in children and adolescents: international survey. BMJ. 2007;335:194–202.
23. Horsthuis K, Bipat S, Stokkers C, et al. Magnetic resonance imaging for evaluation of disease activity in Crohn's disease: a systematic review. Eur Radiol. 2009;19:1450–60.
24. Hyams J, Ferry G, Mandel F, et al. Development and validation of paediatric Crohn's disease activity index. J Pediatr Gastroenterol Nutr. 1991;12:439–47.
25. Hyams J, Markowitz J, Otley A, et al. Evaluation of the pediatric Crohn disease activity index: a prospective multicenter experience. J Pediatr Gastroenterol Nutr. 2005;41:416–21.

26. Vermeire S, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? Gut. 2006;55:426–31.
27. Solem C, Loftus E, Tremaine W, et al. Correlation of C-reactive protein (CRP) with clinical, radiographic, and endoscopic activity in inflammatory bowel disease (IBD). Inflamm Bowel Dis. 2005;11:707–12.
28. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc. 2004;60: 505–12.
29. Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. Am J Gastroenterol. 2010;105:162–9.
30. Girometti R, Zuiani C, Toso F, et al. MRI scoring system including dynamic motility evaluation in assessing the activity of Crohn's disease of the terminal ileum. Acad Radiol. 2008;15: 153–64.
31. Borrelli O, Cordischi L, Cirulli M, et al. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomised controlled open-label trial. Clin Gastroenterol Hepatol. 2006;4:744–53.
32. Yamamoto T, Nakahigashi M, Umegae S, et al. Impact of elemental diet on mucosal inflammation in patients with active Crohn's disease: cytokine production and endoscopic and histological findings. Inflamm Bowel Dis. 2005;11:580–8.
33. Buchanan E, Gaunt W, Cardigan T, et al. The use of exclusive enteral nutrition for induction of remission in children with Crohn's disease demonstrates that disease phenotype does not influence clinical remission. Aliment Pharmacol Ther. 2009;30: 501–7.
34. Zachos M, Tondeur M, Griffiths A. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2007
35. Rutgeerts P, Diamond RH, Bala M, et al. Scheduled maintenance treatment with infliximab is superior to episodic treatment for the healing of mucosal ulceration associated with Crohn's disease. Gastrointest Endosc. 2006;63:433–42.
36. Mantzaris GJ, et al. Azathioprine is superior to budesonide in achieving and maintaining mucosal healing and histologic remission in steroid-dependent Crohn's disease. Inflamm Bowel Dis. 2009;15:375–82.
37. D'Haens G, Geboes K, Rutgeerts P. Endoscopic and histologic healing of Crohn's (ileo-) colitis with azathioprine. Gastrointest Endosc. 1999;50:667–71.
38. D'Haens G, Geboes K, Ponette E, Penninckx F, Rutgeerts P. Healing of severe recurrent ileitis with azathioprine therapy in patients with Crohn's disease. Gastroenterology. 1997;112:1475–81.
39. Sandborn WJ, et al. An intravenous loading dose of azathioprine decreases the time to response in patients with Crohn's disease. Gastroenterology. 1995;109:1808–17.
40. Peneau A, Salleron J,Fumery M, et al. P137, long term outcome of pediatric onset Crohn's disease: a population based study. ECCO abstracts 2012.
41. Rutgeerts P, Reinisch W, Thakkar R, et al. Early mucosal healing status predicts long term clinical benefits for adalimumab-treated patients with moderate to severe Crohn's disease. Gastroenterology. 2010;138:s-85.
42. Cosnes J, Bourrier Y, Bouhnik D, et al. Accelerated step care therapy with early azathioprine vs. conventional step-care therapy in Crohn's disease. A randomized study. Gastroenterology. 2012; 142:S-161.