Comparative Effectiveness of Nutritional and Biological Therapy in North American Children with Active Crohn's Disease

Dale Lee, MD, MSCE,[*,†] Robert N. Baldassano, MD,*[*] Anthony R. Otley, MD,[‡] Lindsey Albenberg, DO,*[*] Anne M. Griffiths, MD,[§] Charlene Compher, RD, PhD,[||] Eric Z. Chen, MS,[¶] Hongzhe Li, PhD,[¶] Erin Gilroy, BS,[¶] Lisa Nessel, MSS,[¶] Amy Grant, PhD,[‡] Christel Chehoud, AB,[**] Frederic D. Bushman, PhD,[**] Gary D. Wu, MD,[††] and James D. Lewis, MD, MSCE[¶,††]*

Background: Therapeutic targets in pediatric Crohn's disease include symptoms, quality of life (QOL), and mucosal healing. Although partial enteral nutrition (PEN), exclusive enteral nutritional (EEN), and anti-tumor necrosis factor alpha (anti-TNF) therapy all improve symptoms, the comparative effectiveness of these approaches to improve QOL and achieve mucosal healing has not been assessed prospectively.

Methods: In a prospective study of children initiating PEN, EEN, or anti-TNF therapy for Crohn's disease, we compared clinical outcomes using the Pediatric Crohn's Disease Activity Index (PCDAI), QOL (IMPACT score), and mucosal healing as estimated by fecal calprotectin (FCP). PCDAI, IMPACT, FCP, and diet (prompted 24-h recall) were measured at baseline and after 8 weeks of therapy.

Results: We enrolled 90 children with active Crohn's disease (PCDAI, 33.7 ± 13.7; and FCP, 976 ± 754), of whom 52 were treated with anti-TNF, 22 with EEN, and 16 with PEN plus ad lib diet. Clinical response (PCDAI reduction ≥15 or final PCDAI ≤10) was achieved by 64% on PEN, 88% EEN, and 84% anti-TNF (test for trend $P = 0.08$). FCP ≤250 μg/g was achieved with PEN in 14%, EEN 45%, and anti-TNF 62% (test for trend $P = 0.001$). Improvement in overall QOL was not statistically significantly different between the 3 groups ($P = 0.86$). However, QOL improvement was the greatest with EEN in the body image ($P = 0.03$) domain and with anti-TNF in the emotional domain ($P = 0.04$).

Conclusions: Although PEN improved clinical symptoms, EEN and anti-TNF were more effective for decreasing mucosal inflammation and improving specific aspects of QOL.

(Inflamm Bowel Dis 2015;21:1786–1793)

Key Words: enteral nutrition, pediatric Crohn's disease, anti-TNF, mucosal healing

Historically, the goals of treatment in children with Crohn's disease (CD) were to improve symptoms and quality of life (QOL), optimize growth, and to support a return to normal functioning while minimizing side effects. Recently, increased attention has been given to mucosal healing, which is associated with sustained clinical remission, reduced surgical rates, and

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.ibdjournal.org).

Received for publication January 30, 2015; Accepted March 10, 2015.

From the *Department of Pediatrics, Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; †Department of Pediatric, Division of Gastroenterology and Nutrition Seattle Children's Hospital, Seattle, Washington; and University of Washington; ‡Department of Pediatrics, IWK Health Centre, Halifax, NS, Canada; §Department of Pediatrics, Division of Gastroenterology, Hepatology and Nutrition, Hospital for Sick Children, University of Toronto, Toronto, ON, Canada; ||School of Nursing, University of Pennsylvania, Philadelphia, Pennsylvania; ¶Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; **Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; and ††Department of Medicine, Division of Gastroenterology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania.

Supported by NIH Grants: T32-DK007740, UH3-DK083981, K24-DK078228; Penn Digestive Disease Center (P30 DK050306), The Joint Penn-CHOP Center for Digestive, Liver, and Pancreatic Medicine, The Penn-CHOP Microbiome Program.

J. D. Lewis has received research funding from Centocor, Shire, Takeda, and Nestec Ltd., served as a consultant for Prometheus, Shire, Pfizer, Lilly, Janssen, AbbVie, Immune Pharmaceuticals, Takeda, Merck, AstraZeneca, Amgen, Rebiotix, and MedImmune, and received honorarium from Nestle Nutrition Institute for organizing and speaking in a scientific symposium. R. N. Baldassano has served on the pediatric advisory board for Janssen Pharmaceuticals, Takeda Pharmaceuticals, and Abbvie, Inc. A. M. Griffiths has received research funding and clinical program support from Abbvie and Janssen and has served as consultant for Abbvie, Ferring, Janssen, Nestle, and Receptos. A. R. Otley has received research funding from Janssen, Abbvie, Astra Zeneca, Shire, and Optimer and served as a consultant for Medunik Canada, and Nestle. He has served on the pediatric advisory board for Janssen, Abbvie, and Nestle. G. D. Wu is a member of scientific advisory boards for Janssen, Rebiotix, and Chr. Hansen and has received an honorarium from Nestle Nutrition Institute for organizing and speaking in scientific symposia. F. D. Bushman has served as a consultant for Merck. The remaining authors have no conflicts of interest to disclose.

Reprints: James D. Lewis, MD, MSCE, 720 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104 (e-mail: lewisjd@upenn.edu).

DOI 10.1097/MIB.0000000000000426

Published online 12 May 2015.

avoidance of corticosteroids.[1] Unfortunately, symptoms and mucosal inflammation correlate poorly.[2,3] Similarly, QOL includes domains that extend beyond symptoms included in standard disease activity measures. This is particularly relevant when considering therapies that result in a state of chronic immunosuppression or nutrition-based interventions that require behavioral changes. Thus, symptoms, mucosal inflammation, and QOL are important outcomes.

Although immunosuppressive therapies, such as anti-tumor necrosis factor alpha (anti-TNF) therapy, are the primary treatment of pediatric CD in the United States, enteral nutritional (EN) therapy is commonly used to induce remission in children from Canada, Australia, Japan, and Europe.[4,5] Both exclusive enteral nutritional (EEN) therapy and anti-TNF therapy can induce clinical remission and mucosal healing in children with CD.[6,7] In addition to potentially avoiding immunosuppression, EEN is associated with improved nutrition and growth parameters, bone metabolism, and muscle mass.[8,9]

Compared with EEN, partial enteral nutrition (PEN) with an unrestricted diet is more appealing to patients since table foods can also be consumed. PEN seems to offer symptomatic benefit, but the effect on QOL and mucosal healing has not been well characterized.[10,11] The balance between therapeutic effectiveness, risk of adverse events, and QOL is an important consideration in children with CD. As part of a larger study assessing the impact of EEN, PEN, and anti-TNF therapy on the composition of the gut microbiota, we assessed clinical outcomes, mucosal healing, and QOL.

METHODS

Study Setting and Participants

Children and young adults less than 22 years of age were enrolled at the time of initiation of EN or anti-TNF therapy for treatment of active CD (defined as the Pediatric Crohn's Disease Activity Index [PCDAI] >10) at The Hospital for Sick Children in Toronto, ON, Canada; IWK Health Centre, Halifax, NS, Canada; and the Children's Hospital of Philadelphia, Pennsylvania. Participants in this observational cohort study were prescreened for eligibility and recruited from clinic or during inpatient hospitalization. Exclusion criteria included presence of an ostomy, treatment with probiotics within 2 weeks of initiating EN, treatment with anti-TNF therapy within 8 weeks of starting EN, or treatment with EN within 1 week of initiating anti-TNF therapy. The study protocol was approved by the institutional review boards at all participating institutions. Informed consent was obtained from all young adults and the parents/guardians of children less than 18 years of age.

Treatments

The decision to initiate participants with active CD on either anti-TNF therapy or EN therapy was made by the treating physician. Anti-TNF therapy was infliximab in all except for 1 child who received adalimumab; standard loading regimens were used. Studies on EN therapy have not demonstrated a difference in outcome by formula type.[12] As such, EN therapy was initiated per institutional protocol for choice of formula, route of administration, and proportion of daily calories from table food. Guidance and monitoring for nutritional therapy was per treating institution: EEN was used at the 2 Canadian sites, and PEN with an unrestricted diet was used in Philadelphia.

Assessment of Participants

Each participant was assessed at baseline, 1, 4, and 8 weeks. Baseline and week 8 assessments were performed in person. Week 1 and 4 assessments were completed through telephone. Baseline demographics, anthropometrics, and disease characteristics were evaluated.

The PCDAI was measured at baseline and week 8. Clinical response was defined as a reduction in PCDAI by ≥15 points or final PCDAI ≤10; clinical remission was defined as PCDAI ≤10 at week 8. In the primary analysis, we did not impute response or remission status if the final PCDAI was missing (n = 10). Two additional sensitivity analyses were performed—one with the categorization of participants missing final PCDAI as nonresponders and the second with imputation of clinical response status from symptoms (see Methods, Supplemental Digital Content 1, http://links.lww.com/IBD/A879).

Fecal calprotectin (FCP) concentration was measured (Genova Diagnostics, Asheville, NC) at all 4 visits as a marker of intestinal mucosal inflammation. FCP is highly correlated with endoscopic findings and is a useful surrogate marker for mucosal healing after initiation of medications in active CD.[13,14] There is no single standard to define mucosal healing with FCP,[15–17] although ≤50 μg/g is used to distinguish noninflammatory from inflammatory conditions, and a recent meta-analysis identified 250 μg/g as the optimal cutpoint for endoscopically defined inflammation among patients with inflammatory bowel disease.[18,19] For this study, the final FCP was assessed at the thresholds of ≤50 μg/g among those with baseline FCP >50 μg/g, ≤250 μg/g among those with baseline FCP >250 μg/g, and >50% reduction from baseline. If FCP at baseline was missing (n = 2), FCP at week 1 was used to impute the pretreatment level. If FCP at week 8 was missing (n = 8), FCP at week 4 was used (n = 6). If FCP at both weeks 4 and 8 were missing (n = 2), final FCP ≤250 μg/g and ≤50 μg/g status were noted as "missing."

The IMPACT-III questionnaire is a validated disease-specific measure of QOL in pediatric inflammatory bowel disease and was evaluated at baseline and 8 weeks.[20,21] From 35 questions, a total score and 6 specific domain subscores were assessed: bowel symptoms, systemic symptoms, emotional functioning, social functioning, body image, and treatment. IMPACT-III QOL scores range from 0 (worst) to 100 (best). Missing values from the IMPACT-III questionnaire were accounted for by reweighting the total and domain scores by the number of questions answered.

After each study visit, a research bionutritionist conducted three 24-hour dietary recalls, 2 on weekdays and 1 on a weekend

day through telephone. The validated multipass procedures were used to optimize collection of complete and accurate quantitative food intake from participants with assistance from parents as needed. Intake of calories, macronutrients, vitamins, and food groups was assessed using the Nutrition Data System for Research 2012 from the University of Minnesota. Expected energy requirement (EER) was calculated from Dietary Reference Intakes from the Institute of Medicine and based on age, sex, height, weight, and the assumption of a "low active" physical activity level.[22] Total average daily caloric intake was determined at each visit and divided by EER to obtain energy intake as percent intake of EER (%EER).

Statistical Analysis

Analyses were conducted using STATA 12.0 (Statacorp, College Station, TX). The study protocol targeted the recruitment of 50 subjects in each arm (EN and anti-TNF) based on anticipated sample sizes needed to compare microbial composition between the 2 treatment groups. With a sample size of 38 subjects treated with EN (22 EEN and 16 PEN) and 52 with anti-TNF, assuming 14% mucosal healing rate with PEN, this study would have 80% power to detect a 48% and 39% absolute increase with EEN and anti-TNF, respectively.

Differences in mean values were assessed using Student's *t* test, the Wilcoxon rank-sum test, or the Kruskall–Wallis test as appropriate. Group differences in categorical variables were assessed with Fisher's exact test. Tests for trend assumed a rank order of PEN, EEN, anti-TNF and were conducted using logistic regression. For evaluating change over time in PCDAI, FCP, and IMPACT-III scores, a last observation carried forward approach was used. Analysis of covariance was used to adjust for baseline differences across groups.

To assess for confounders when comparing clinical response rates and mucosal healing between the treatment groups, we generated a disease risk score using logistic regression that was derived from the baseline characteristics of the entire cohort as described by Cadarette (see Methods, Supplemental Digital Content 1, http://links.lww.com/IBD/A879).[23] We included in the risk score all variables with a *P*-value <0.25 using a backward-selection procedure (see Table, Supplemental Digital Content 2, http://links.lww.com/IBD/A880). Regression models were then adjusted for the disease risk score.

Exploratory analyses were conducted to evaluate the relationship between consumption of specific food groups (measured at week 4) and disease course. These models were tested for confounding by baseline FCP (log transformed), clinical symptoms, and caloric intake (%EER) using linear regression.

RESULTS

Comparison of Groups at Baseline

A total of 90 participants enrolled in the study, with 16 initiating PEN, 22 EEN, and 52 anti-TNF (Table 1). Age was similar between the 3 groups, but median disease duration was shorter in the EN groups ($P = 0.001$; PEN 0.11 yr, EEN 0.03 yr, and anti-TNF 0.72 yr), and percentage male was also greater in the EN therapy groups. Disease distribution was similar with most subjects having ileal and colonic disease. Active perianal disease at study enrollment was present in 0 subjects treated with PEN, 3 with EEN, and 8 subjects with anti-TNF. One additional EEN patient and 2 anti-TNF treated patients had a history of perianal disease. Baseline PCDAI was lowest in the anti-TNF group but similar in the PEN and EEN groups (30.2 $\pm$12.0, 37.6 $\pm$ 19.3, and 38.8 $\pm$ 11.0, respectively; $P = 0.01$). Baseline FCP was not different across the 3 groups. Baseline systemic steroid exposure was present in 10 subjects initiating PEN (63%), 0 initiating EEN, and 23 (44%) initiating anti-TNF. Height Z-score was similar across the 3 groups, but mean weight Z-score was lower in PEN-treated patients ($P = 0.04$).

Disease Therapy

Subjects initiating PEN were started on Peptamen Jr (standard or 1.5) or Peptamen 1.5 (Nestle, Vevey, Switzerland), whereas those initiating EEN were mostly divided among Modulen (Nestle) and Osmolite (Abbott Nutrition, Columbus, OH) (see Table, Supplemental Digital Content 3, http://links.lww.com/IBD/A881). In the PEN group, 1 subject discontinued formula feedings early because of poor tolerance of therapy. In the EEN group, 2 subjects stopped early because of poor tolerance of feeds, and 2 subjects discontinued formula feedings either because of loss of interest or the decision to stop EEN as therapy. For the PEN group, the proportion of subjects with systemic steroid exposure did not change from baseline to week 8, but for the anti-TNF group steroid use decreased (44%–25%; $P = 0.06$; see Table, Supplemental Digital Content 4, http://links.lww.com/IBD/A882). The participants in the EEN group had no documented steroid exposure over the 8-week study period. Thiopurine exposure was low at baseline for the EN groups (0% PEN, 5% EEN), but by week 8, it increased to 27% ($P = 0.10$) of participants in the EEN group and did not change for PEN. Thiopurine exposure in the anti-TNF group (13%) did not change over the study. Methotrexate exposure did not change from baseline for any of the groups.

Comparison of Nutrition Intake

Caloric intake (%EER) was not different between the groups at baseline (Table 1), but by week 4, it was significantly greater in the PEN group and lowest in the anti-TNF group (Table 2). Participants on PEN received a mean 47.0% $\pm$ 13.5% (range, 10%–75%) of daily calories from table food (not formula), whereas the EEN group consumed 10.2% $\pm$ 5.7% (range, 0.5%–21%) of their daily calories from table food (which consisted mostly of clear liquids) ($P < 0.0001$). Only 1 participant in the PEN group consumed table food in the range of calories consumed by the EEN group, with the next lowest percent of table food consumption in the PEN group being 35% of

TABLE 1. Baseline Demographics and Disease Characteristics

	PEN (n = 16)	EEN (n = 22)	TNF (n = 52)	*P*
Age, yr	12.0 (8.6–16.6)	12.5 (7.2–17.8)	13.9 (3.8–19.5)	0.25
Disease duration, yr	0.1 (0–2.8)	0.03 (0–1.1)	0.7 (0–7.2)	0.001
Male, n (%)	14 (88)	16 (73)	24 (46)	0.005
Previous surgery, n (%)	1 (6)	0	5 (9.6)	0.54
Disease location, n (%)				
Upper	7 (44)	16 (73)	28 (54)	0.17
Ileum	16 (100)	21 (95)	43 (83)	0.08
Colon	15 (94)	19 (86)	50 (96)	0.30
Perianal	1 (6)	4 (18)	10 (19)	0.47
Penetrating disease, n (%)	0	1 (5)	3 (6)	0.62
Stricturing disease, n (%)	1 (6)	0	5 (9.6)	0.32
Antibiotics within 6 mo, n (%)	7 (44)	5 (23)	37 (71)	<0.001
PCDAI	37.6 ± 19.3	38.8 ± 11.0	30.2 ± 12.0	0.01
FCP	998 ± 826	1028 ± 613	948 ± 795	0.65
Medications, n (%)				
Antibiotics	4 (25)	1 (5)	21 (40)	0.007
Oral 5-ASA	11 (69)	1 (5)	33 (63)	<0.001
Rectal 5-ASA	0	0	2 (4)	0.47
Thiopurines	0	1 (5)	7 (13)	0.18
Methotrexate	1 (6)	1 (5)	4 (8)	0.88
Systemic steroid	10 (63)	0	23 (44)	<0.001
Rectal steroid	0	0	1 (2)	0.69
%EER	95.1 ± 40.4	81.5 ± 32.4	88.9 ± 30.2	0.54
Height Z-score	−0.71 ± 1.27	−0.53 ± 1.15	−0.55 ± 0.84	0.68
Weight Z-score	−1.25 ± 0.89	−1.14 ± 1.32	−0.63 ± 1.22	0.04
BMI Z-score	−1.47 ± 2.04	−1.35 ± 1.36	−0.51 ± 1.42	0.01
IMPACT total score, median (IQR)	61 (52–78)	64 (56–75)	64 (55–75)	0.99
Bowel subscore	64 (43–75)	57 (32–75)	57 (48–71)	0.69
Systemic	63 (25–83)	50 (33–67)	50 (25–75)	0.64
Emotional	59 (43–68)	66 (43–83)	61 (45–79)	0.78
Social function	72 (67–83)	73 (71–85)	73 (64–78)	0.76
Body image	71 (54–75)	58 (58–75)	67 (50–83)	0.79
Treatment	63 (42–83)	75 (67–92)	67 (50–75)	0.21

Median (range or IQR) or mean ± SD.
ASA, aminosalicylic acid; IQR, interquartile range.

TABLE 2. Daily Caloric Intake at 4 Weeks Among Participants Treated with PEN, EEN, or Anti-TNF

	PEN	EEN	TNF	*P* (PEN versus EEN)
%EER	150.8 ± 36.2	128.2 ± 19.9	92.2 ± 32.7	0.02
%EER from formula	77.7 ± 14.2	115.3 ± 20.8	—	<0.0001
%EER from food	72.9 ± 25.5	12.9 ± 6.9	—	<0.0001
%Kilocalories from food	47.0 ± 13.5	10.2 ± 5.7	—	<0.0001

TABLE 3. Changes from Baseline to Week 8 Among Participants Treated with PEN, EEN, or Anti-TNF

	PEN	EEN	TNF	ANCOVA P^a	P^a (PEN versus EEN)	P^a (PEN versus TNF)	P^a (EEN versus TNF)
PCDAI	−17.7 ± 20.3[b]	−25.5 ± 17.0[b]	−19.5 ± 15.5[b]	0.43	0.53	0.61	0.20
FCP	−380 ± 660[b]	−682 ± 678[b]	−622 ± 678[b]	0.68	0.88	0.43	0.75
Weight Z-score	0.76 ± 0.66[b]	0.70 ± 0.57[b]	0.38 ± 0.40[b]	0.03	0.98	0.04	0.03
BMI Z-score	1.24 ± 1.36	1.13 ± 0.96	0.48 ± 0.56	0.005	0.34	0.07	0.002
IMPACT	6.2 ± 9.6[b]	11.0 ± 12.1[b]	10.5 ± 13.8[b]	0.86	0.77	0.85	0.58
IMPACT subscores							
Bowel	5.1 ± 13.5	14.4 ± 22.8[b]	14.4 ± 20.3[b]	0.09	0.25	0.03	0.33
Systemic	13.0 ± 23.4[b]	33.0 ± 27.3[b]	21.6 ± 26.1[b]	0.08	0.03	0.21	0.14
Emotional	8.6 ± 13.6[b]	9.4 ± 17.4[b]	10.4 ± 16.4[b]	0.04	0.09	0.01	0.33
Social	3.8 ± 7.5	6.0 ± 12.5[b]	8.0 ± 12.0[b]	0.49	0.71	0.56	0.26
Body image	4.7 ± 12.9	12.9 ± 13.8[b]	2.7 ± 16.6	0.03	0.26	0.31	0.01
Treatment	7.3 ± 16.1	3.0 ± 15.3	7.5 ± 18.7[b]	0.99	0.90	0.88	1.0

[a]Adjusted for baseline value.
[b]$P < 0.05$ for change.

total daily calories. At week 4, children in the EEN group consumed a highly restricted diet in addition to formula, which consisted mostly of clear liquids: noncitrus fruit juice, frozen nondairy desserts, sweetened soft drinks, soup broth, unsweetened water, and nonchocolate candy. Intake of foods was similar between the PEN and anti-TNF groups, and the food groups with the largest average number of servings consumed per day were refined and some whole grain products (mostly breads), vegetables, and poultry (see Table, Supplemental Digital Content 5, http://links.lww.com/IBD/A883). Compared with the PEN group, the anti-TNF group consumed greater mean daily servings of whole grains ($P = 0.01$), milk ($P = 0.01$), salad dressing ($P = 0.05$), and sugar/candy ($P = 0.05$). Percent Dietary Reference Intake of protein and carbohydr7ates and mean intake of grams of fat per kilogram body weight were different across all 3 treatment groups ($P < 0.001$ for each; see Table, Supplemental Digital Content 6, http://links.lww.com/IBD/A884).

Comparison of Clinical Outcomes

At baseline, PCDAI was higher in the nutritional therapy groups than in the anti-TNF group ($P = 0.01$), whereas FCP was similar (Table 1). Over 8 weeks, all 3 treatment groups had a significant decrease in PCDAI and FCP ($P < 0.05$ for all comparisons; Table 3). After adjusting for the disease risk score, a trend of increasing proportion of subjects achieving clinical response was seen from PEN to EEN to anti-TNF (adjusted $P = 0.08$). Sensitivity analysis with imputation of clinical response status demonstrated similar results, although the test for trend reached statistical significance in both sensitivity analyses (see Table, Supplemental Digital Content 7, http://links.lww.com/IBD/A885). Subgroup analysis excluding subjects classified as having no further linear growth potential (men >17 yr and women >15 yr) demonstrated outcomes similar to the primary analysis. In the subgroup analysis, in the comparison of PEN versus anti-TNF for the outcome of clinical

TABLE 4. Treatment Outcomes Over 8 Weeks Among Participants Treated with PEN, EEN, or Anti-TNF

Outcome, n (%)	PEN	EEN	Anti-TNF	P^a (PEN versus EEN)	P^a (PEN versus TNF)	P^a (EEN versus TNF)	Test for Trend P^a
Clinical remission	7 (50)	13 (76)	36 (73)	0.03	0.15	0.33	0.29
Clinical response	9 (64)	15 (88)	41 (84)	0.08	0.04	0.78	0.08
FCP ≤50 μg/g	0	1 (5)	14 (30)	NA[b]	NA[b]	0.03	0.01
FCP ≤250 μg/g	2 (14)	10 (45)	26 (62)	0.04	0.02	0.13	0.001
FCP >50% reduction	7 (47)	14 (64)	34 (72)	0.15	0.02	0.51	0.03

[a]Outcomes are adjusted for disease risk score.
[b]Outcome FCP ≤50 μg/g: unadjusted *P*-values for PEN versus TNF and PEN versus EEN are 0.014 and 1.0, respectively.

response, statistical significance was attenuated (64% versus 84%; $P = 0.07$).

Each group had a significant decrease in FCP concentration (Table 3). Subjects in the anti-TNF group had the highest percentage achievement of FCP ≤250 μg/g (Table 4; PEN 14%, EEN 45%, anti-TNF 62%). The proportion of subjects achieving FCP ≤50 μg/g, FCP ≤250 μg/g, and >50% reduction in FCP again displayed a trend toward increasing rates of success from PEN to EEN to anti-TNF ($P = 0.01$, $P = 0.001$, and $P = 0.03$, respectively; Table 4).

No association between week 8 outcomes and percent of daily calories coming from food were present for the PEN group ($P = 0.99$ and $P = 0.95$ for clinical response and FCP ≤ 250 μg/g, respectively). For the EEN group, greater percent of daily calories coming from clear liquids and hard candy was associated with a greater likelihood of achieving clinical response and FCP ≤250 μg/g ($P = 0.04$ and $P = 0.06$, respectively).

Though baseline clinical disease severity was different by treatment group, the relationship of treatment group with clinical and FCP outcomes was relatively similar when stratified by baseline clinical severity (test for interaction by disease severity $P = 0.42$ for clinical remission and $P = 0.72$ for FCP ≤250 μg/g) (Fig. 1). Subjects in the PEN group with systemic steroid exposure at baseline had similar outcomes to those without steroid exposure (see Table, Supplemental Digital Content 8, http://links.lww.com/IBD/A886). In the anti-TNF group, children without steroid exposure at baseline had better outcomes for clinical response and trends for better response for the FCP outcomes and clinical remission. Active perianal disease at baseline was not associated with differential clinical or FCP outcomes for any of the 3 groups.

Comparison of QOL

At baseline, total IMPACT-III and domain scores were similar across the 3 treatment groups (Table 1). Each group had a significant increase in total IMPACT score over the 8-week study ($P < 0.05$; Table 3). Subjects who achieved clinical remission in the anti-TNF group demonstrated a larger increase in total IMPACT score compared with subjects not in remission ($P = 0.01$), whereas subjects achieving remission in the PEN and EEN groups did not have statistically significantly larger increases in IMPACT score ($P = 0.37$ and $P = 0.12$, respectively). For each treatment group, improvements in IMPACT were similar between subjects who did and did not achieve a final FCP ≤250 μg/g ($P \geq 0.10$ for each).

Relative to PEN, the EEN group exhibited a larger improvement in systemic symptoms ($P = 0.03$; Table 3). With additional adjustment for clinical remission status at week 8, systemic symptoms improved more with EEN than with anti-TNF ($P = 0.01$); otherwise the relationships were either similar to the primary analysis or attenuated (data not shown). Although EEN is more restrictive of foods than PEN, the social functioning and treatment domains were similar ($P = 0.71$ and $P = 0.90$). Improvement in the body image QOL domain was similar between the EEN and PEN groups ($P = 0.26$), yet greater for EEN compared with the anti-TNF group ($P = 0.01$). Adjusting for clinical remission status, the associations for social, treatment, and body image domains did not change.

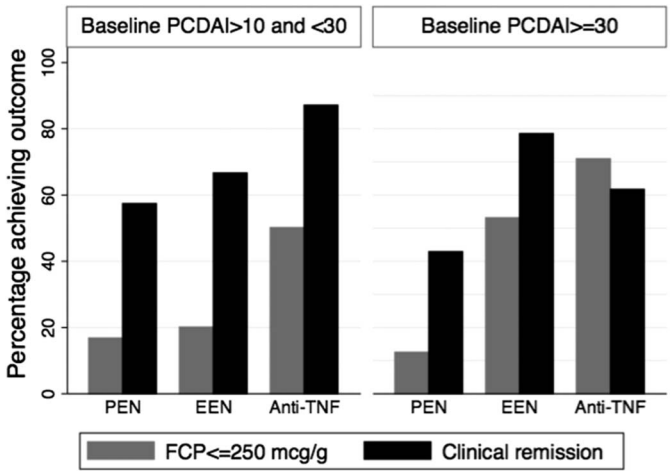

FIGURE 1. Rates of clinical remission and reduction in FCP with PEN, EEN, and anti-TNF therapy stratified by baseline clinical disease activity.

Exploratory Analysis of Food Intake and Response Among PEN and Anti-TNF Groups

Participants treated with PEN who achieved a >50% reduction in FCP consumed fewer daily servings of red meat than those with lower reduction in FCP: 0.4 ± 0.4 versus 1.7 ± 1.1 servings per day ($P = 0.01$ unadjusted, $P = 0.03$ adjusted for symptoms; see Table, Supplemental Digital Content 9, http://links.lww.com/IBD/A887). Likewise, poultry consumption was lower in those treated with PEN who achieved a >50% reduction in FCP, although this was not statistically significant (1.2 ± 1.1 versus 2.5 ± 1.7 servings per day, $P = 0.09$). Among participants receiving PEN, consumption of red meat and poultry was not statistically different according to whether clinical remission was achieved ($P = 0.84$ and $P = 0.39$, respectively). In the anti-TNF group, no significant differences in red meat or poultry intake were noted between those who did versus did not achieve >50% reduction in FCP ($P = 0.37$ and $P = 0.51$, respectively). Adjustment for %EER produced similar results (data not shown).

DISCUSSION

The choice between PEN, EEN, and anti-TNF therapy in the treatment of children with CD should be driven by an understanding of both the benefits and harms of therapy. Some patients, parents, and clinicians are attracted to nutrition-based therapies that do not suppress the immune system, whereas others shy away from these therapies because of the challenges in administration and disruption of normal lifestyle. This study demonstrates that each of the therapies improved symptoms of CD, but EEN and anti-TNF therapies are superior to PEN for inducing mucosal healing. Furthermore, EEN provided similar to

greater improvement in QOL in each measured domain. Because the PEN group consumed nearly as many calories per day through formula as the EEN group and a similar ad lib diet as the anti-TNF group, these data imply that the efficacy of EEN may be a consequence of elimination of table food rather than providing a uniquely therapeutic method of delivering nutrients.

There are limited data directly comparing PEN, EEN, and anti-TNF for key clinical outcomes. Previous studies have compared different enteral formulas and EEN versus steroids. Choice of formula has not impacted the efficacy of enteral nutrition,[12] and steroids have been superior to EEN for induction of clinical remission, in part due to issues of adherence with EEN.[24,25] In our study, the percentage of children with CD achieving FCP ≤250 was greatest for anti-TNF followed by EEN then PEN. Corticosteroid use did not seem to impact the relative effectiveness. Given the documented importance of mucosal healing on clinical outcomes, these data support the use of EEN over PEN for patients who choose EN as an induction regimen[10] and the need to confirm mucosal healing.

Participants in all 3 treatment groups had significant improvements in QOL, which is similar to the consistent improvements seen in PCDAI scores. Compared with participants receiving PEN, those receiving EEN had greater improvements in QOL for systemic symptoms. Despite the highly restrictive nature of EEN, participants did not have lower social functioning or greater treatment-associated impairment. Similar to a previous report, our study demonstrates an association between improved QOL and clinical remission status but not mucosal healing.[26] These data should be considered when describing treatment options to children with CD and their parents.

Sigall-Boneh et al[27] have hypothesized that EN therapy is effective because of the exclusion of table foods. The finding that greater percent of daily calories coming from food (clear liquids and hard candy) was associated with a greater likelihood of achieving clinical response and FCP ≤250 μg/g in the EEN group suggests that the type of foods eaten may play a more important role than the quantity of table foods eaten. Sigall-Boneh et al[27] have recently published data from an open-label study of PEN with a restricted diet and demonstrated the ability of this dietary therapy to induce clinical remission in 70% of children and 69% of adults with active CD. This suggests a harmful effect of specific table foods but will require further study.

In an exploratory analysis of food consumption in the PEN group of our study, the association between decreased consumption of poultry and red meat and greater reduction in FCP suggests that a certain constituent of these foods may increase inflammation. In rat models of colitis, iron supplementation has been found to be associated with evidence of oxidative stress and increased intestinal inflammation.[28] Iron may be one of the constituents in food, particularly in meat and poultry, that drives ongoing intestinal inflammation, but it is likely that numerous components of the diet are involved in the etiology and perpetuation of CD.

In this study, treatment with PEN or EEN was not assigned randomly. Rather, all participants treated at 1 institution received PEN, whereas at the other 2 centers, EEN was prescribed. We adjusted for important clinical variables using a disease risk score derived from the same study population. However, unmeasured confounders could contribute to the differences in outcomes. The PCDAI is a validated measure in pediatrics, but 3 study participants (all from anti-TNF group) were older than 18 years. Although this could imply inability to receive points for height–velocity deceleration, the short duration of this study precludes measurable changes in linear growth. Differential steroid exposure is possibly a surrogate for more refractory disease, but stratified analysis showed similar or superior PCDAI and FCP outcomes among the patients without steroid exposure in the PEN and anti-TNF groups. Although steroids were able to be weaned in subjects in the anti-TNF group, subjects on PEN with an unrestricted diet continued to require steroids. Steroid sparing effects of anti-TNF therapy have been previously described.[7,29] Future studies are needed to assess whether EEN can be used to allow discontinuation of steroids in patients with steroid-dependent CD.

The analysis of food intake is subject to the limitations of dietary analysis including challenges in capturing forgotten food items and method of preparation due to participant recall bias.[30] However, we obtained three 24-hour recalls prompted by a research bionutritionist for each visit using validated methods to obtain typical food intake. A potential limitation of the study design is the absence of endoscopic or radiographic imaging to assess for mucosal healing. Our study used FCP as a surrogate for mucosal healing. Although FCP is not perfectly correlated with endoscopic assessment of disease activity, reduction in FCP after anti-TNF induction therapy has been associated with endoscopically assessed mucosal healing and clinical disease course.[31]

Our study has demonstrated the ability of EEN, a highly restrictive, nutrition-based therapy to alter ongoing intestinal inflammation and improve aspects of QOL in children with CD. Anti-TNF therapy was as, or more, effective and allowed the consumption of table foods that were associated with worse outcomes in patients receiving PEN. Our data suggest that EEN is likely effective based on exclusion of "harmful" factors rather than through more effective delivery of a specific nutrient and that immunosuppression with anti-TNF therapy is able to overcome the effect of dietary exposure. The mechanism by which exclusion of a harmful factor impacts disease needs to be further defined but could entail alterations of the gut microbiome or metabolome. Current efforts are underway to study the effect of restricted table food-based diets on active CD, but the inherent heterogeneity in table foods creates challenges. Until large-scale studies can inform the most effective dietary approach, for patients who prefer treatment with a nutrition-based therapy, EEN seems superior to PEN for improvement in CD-related symptoms, QOL, and reduction in intestinal inflammation.

ACKNOWLEDGMENTS

Author contributions: D. Lee contributed in study design, data analysis, and authorship of the article. He has approved the final draft submitted; R. N. Baldassano contributed in study

design and authorship of the article. He has approved the final draft submitted; A. R. Otley contributed in study design, data analysis, and authorship of the article. He has approved the final draft submitted; A. M. Griffiths contributed in study design, data analysis, and authorship of the article. She has approved the final draft submitted; C. Compher contributed to data analysis and authorship of the article. She has approved the final draft submitted; L. Albenberg contributed to data analysis and authorship of the article. She has approved the final draft submitted; E. Z. Chen contributed to data analysis and authorship of the article. He has approved the final draft submitted; H. Li contributed to study design, data analysis, and authorship of the article. He has approved the final draft submitted; E. Gilroy contributed in data collection and authorship of the article. She has approved the final draft submitted; L. Nessel contributed in data collection, and authorship of the article. She has approved the final draft submitted; A. Grant contributed in study design, data analysis, and authorship of the article. She has approved the final draft submitted; C. Chehoud contributed to data analysis and authorship of the article. She has approved the final draft submitted; F. D. Bushman contributed in obtaining funding, study design, data analysis, and authorship of the article. He has approved the final draft submitted; G. D. Wu contributed in obtaining funding, study design, data analysis, and authorship of the article. He has approved the final draft submitted; J. D. Lewis contributed in obtaining funding, study design, data collection, data analysis, and authorship of the article. He has approved the final draft submitted.

REFERENCES

1. 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;138:463–468; quiz e10–e11.
2. Ruemmele FM, Hyams JS, Otley A, et al. Outcome measures for clinical trials in paediatric IBD: an evidence-based, expert-driven practical statement paper of the paediatric ECCO committee. *Gut*. 2014;3:438–446.
3. De Cruz P, Kamm MA, Prideaux L, et al. Mucosal healing in Crohn's disease: a systematic review. *Inflamm Bowel Dis.* 2013;19:429–444.
4. Ruemmele FM, Veres G, Kolho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis.* 2014;10:1179–1207.
5. Day AS, Whitten KE, Sidler M, et al. Systematic review: nutritional therapy in paediatric Crohn's disease. *Aliment Pharmacol Ther.* 2008;27:293–307.
6. Borrelli O, Cordischi L, Cirulli M, et al. Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. *Clin Gastroenterol Hepatol.* 2006;4:744–753.
7. Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology*. 2007;132:863–873; quiz 1165–1166.
8. Werkstetter KJ, Schatz SB, Alberer M, et al. Influence of exclusive enteral nutrition therapy on bone density and geometry in newly diagnosed pediatric Crohn's disease patients. *Ann Nutr Metab.* 2013;63:10–16.
9. Whitten KE, Leach ST, Bohane TD, et al. Effect of exclusive enteral nutrition on bone turnover in children with Crohn's disease. *J Gastroenterol.* 2010;45:399–405.
10. Johnson T, Macdonald S, Hill SM, et al. Treatment of active Crohn's disease in children using partial enteral nutrition with liquid formula: a randomised controlled trial. *Gut*. 2006;55:356–361.
11. Takagi S, Utsunomiya K, Kuriyama S, et al. Effectiveness of an "half elemental diet" as maintenance therapy for Crohn's disease: a randomized-controlled trial. *Aliment Pharmacol Ther.* 2006;24:1333–1340.
12. Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev.* 2007;1:CD000542.
13. Lewis JD. The utility of biomarkers in the diagnosis and therapy of inflammatory bowel disease. *Gastroenterology*. 2011;140:1817–1826 e2.
14. Summerton CB, Longlands MG, Wiener K, et al. Faecal calprotectin: a marker of inflammation throughout the intestinal tract. *Eur J Gastroenterol Hepatol.* 2002;14:841–845.
15. D'Haens G, Ferrante M, Vermeire S, et al. Fecal calprotectin is a surrogate marker for endoscopic lesions in inflammatory bowel disease. *Inflamm Bowel Dis.* 2012;18:2218–2224.
16. Sipponen T, Karkkainen P, Savilahti E, et al. Correlation of faecal calprotectin and lactoferrin with an endoscopic score for Crohn's disease and histological findings. *Aliment Pharmacol Ther.* 2008;28:1221–1229.
17. 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;105:162–169.
18. Waugh N, Cummins E, Royle P, et al. Faecal calprotectin testing for differentiating amongst inflammatory and non-inflammatory bowel diseases: systematic review and economic evaluation. *Health Technol Assess.* 2013;17:15–19, 1–211.
19. Lin JF, Chen JM, Zuo JH, et al. Meta-analysis: fecal calprotectin for assessment of inflammatory bowel disease activity. *Inflamm Bowel Dis.* 2014;20:1407–1415.
20. Otley A, Smith C, Nicholas D, et al. The IMPACT questionnaire: a valid measure of health-related quality of life in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr.* 2002;35:557–563.
21. Otley AR, Griffiths AM, Hale S, et al. Health-related quality of life in the first year after a diagnosis of pediatric inflammatory bowel disease. *Inflamm Bowel Dis.* 2006;12:684–691.
22. Institute of Medicine FaNB. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids*. Washington, DC: National Academies Press; 2002.
23. Cadarette SM, Gagne JJ, Solomon DH, et al. Confounder summary scores when comparing the effects of multiple drug exposures. *Pharmacoepidemiol Drug Saf.* 2010;19:2–9.
24. Lindor KD, Fleming CR, Burnes JU, et al. A randomized prospective trial comparing a defined formula diet, corticosteroids, and a defined formula diet plus corticosteroids in active Crohn's disease. *Mayo Clin Proc.* 1992;67:328–333.
25. Malchow H, Steinhardt HJ, Lorenz-Meyer H, et al. Feasibility and effectiveness of a defined-formula diet regimen in treating active Crohn's disease. European Cooperative Crohn's Disease Study III. *Scand J Gastroenterol.* 1990;25:235–244.
26. Afzal NA, Van Der Zaag-Loonen HJ, Arnaud-Battandier F, et al. Improvement in quality of life of children with acute Crohn's disease does not parallel mucosal healing after treatment with exclusive enteral nutrition. *Aliment Pharmacol Ther.* 2004;20:167–172.
27. Sigall-Boneh R, Pfeffer-Gik T, Segal I, et al. Partial enteral nutrition with a Crohn's disease exclusion diet is effective for induction of remission in children and young adults with Crohn's disease. *Inflamm Bowel Dis.* 2014;20:1353–1360.
28. Uritski R, Barshack I, Bilkis I, et al. Dietary iron affects inflammatory status in a rat model of colitis. *J Nutr.* 2004;134:2251–2255.
29. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med.* 2010;362:1383–1395.
30. Fave G, Beckmann ME, Draper JH, et al. Measurement of dietary exposure: a challenging problem which may be overcome thanks to metabolomics? *Genes Nutr.* 2009;4:135–141.
31. Molander P, af Bjorkesten CG, Mustonen H, et al. Fecal calprotectin concentration predicts outcome in inflammatory bowel disease after induction therapy with TNFalpha blocking agents. *Inflamm Bowel Dis.* 2012;18:2011–2017.