Omega-3 Free Fatty Acids for the Maintenance of Remission in Crohn Disease

The EPIC Randomized Controlled Trials

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Context Maintenance therapy for Crohn disease features the use of immunosuppressive drugs, which are associated with an increased risk of infection. Identification of safe and effective maintenance strategies is a priority.

Objective To determine whether the oral administration of omega-3 free fatty acids is more effective than placebo for prevention of relapse of Crohn disease.

Design, Setting, and Patients Two randomized, double-blind, placebo-controlled studies (Epanova Program in Crohn's Study 1 [EPIC-1] and EPIC-2) conducted between January 2003 and February 2007 at 98 centers in Canada, Europe, Israel, and the United States. Data from 363 and 375 patients with quiescent Crohn disease were evaluated in EPIC-1 and EPIC-2, respectively.

Interventions Patients with a Crohn's Disease Activity Index (CDAI) score of less than 150 were randomly assigned to receive either 4 g/d of omega-3 free fatty acids or placebo for up to 58 weeks. No other treatments for Crohn disease were permitted.

Main Outcome Measure Clinical relapse, as defined by a CDAI score of 150 points or greater and an increase of more than 70 points from the baseline value, or initiation of treatment for active Crohn disease.

Results For EPIC-1, 188 patients were assigned to receive omega-3 free fatty acids and 186 patients to receive placebo. Corresponding numbers for EPIC-2 were 189 and 190 patients, respectively. The rate of relapse at 1 year in EPIC-1 was 31.6% in patients who received omega-3 free fatty acids and 35.7% in those who received placebo (hazard ratio, 0.82; 95% confidence interval, 0.51-1.19; $P=.30$). Corresponding values for EPIC-2 were 47.8% and 48.8% (hazard ratio, 0.90; 95% confidence interval, 0.67-1.21; $P=.48$). Serious adverse events were uncommon and mostly related to Crohn disease.

Conclusion In these trials, treatment with omega-3 free fatty acids was not effective for the prevention of relapse in Crohn disease.

Trial Registration clinicaltrials.gov Identifiers: EPIC-1: NCT00613197, EPIC-2: NCT00074542

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EFFECTIVE THERAPY TO MAINtain remission in Crohn disease is an unmet medical need. Although formulations of 5-aminosalicylic acid agents remain widely used for this purpose, strong evidence exists that they are not effective.[1] Immunosuppressive agents such as purine antimetabolites,[2,3] methotrexate,[4] and tumor necrosis factor α antagonists[5-8] are moderately effective for maintaining remission; however, their use is associated with an increased risk of infection.[9-11] Therefore, development of a safe, inexpensive, and effective orally administered agent is a research priority.

See also Patient Page.

Omega-3 free fatty acids are anti-inflammatory substances found in marine fish that have several health benefits. These compounds have been used to treat inflammatory disorders such as rheumatoid

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arthritis[12,13] and IgA nephropathy.[14] Additionally, administration of omega-3 free fatty acids reduces the concentration of serum triglycerides in patients with dyslipidemia[15-17] and decreases the risk of death from cardiac disease.[18-20] However, previous clinical trials that evaluated omega-3 free fatty acids for maintenance of remission in Crohn disease have yielded inconsistent results. Belluzzi et al[21] demonstrated a 33% absolute reduction in the 1-year risk of relapse in patients treated with 2.7 g/d of omega-3 free fatty acids compared with placebo. In contrast, no benefit was observed in a second trial in which patients received 5 g/d of highly concentrated omega-3 free fatty acids.[22] Based on these observations, we conducted 2 large-scale trials of high-dose omega-3 free fatty acids as maintenance therapy in patients with quiescent Crohn disease. Two independent trials were performed, in complementary populations of patients, to meet regulatory expectations.

METHODS

These multicenter, randomized, double-blind, placebo-controlled studies were conducted in Canada, Europe, Israel, and the United States between January 2003 and February 2007. Fifty-one sites participated in Epanova Program in Crohn's Study 1 (EPIC-1), and 47 sites participated in EPIC-2. The institutional review board at each site approved the protocols. All patients provided written informed consent.

Eligible patients were adults with a confirmed diagnosis of Crohn disease and a Crohn's Disease Activity Index (CDAI)[23] score of less than 150 points. In EPIC-1, patients were eligible if they had experienced a disease exacerbation within the past year and were in remission for at least 3 months but not longer than 12 months. In EPIC-2, patients with active disease were treated with a standardized 16-week tapering course of either prednisone[24] or budesonide[25] at initial doses of 40 mg once daily and 9 mg once daily, respectively. Eight weeks after the initiation of corticosteroid treatment, the CDAI score was assessed; if it was less than 150 points, the patient was eligible for randomization. At this time, patients were receiving either 20 mg/d of prednisone or 6 mg/d of budesonide.

Patients were not eligible if they were allergic or intolerant of omega-3 free fatty acids or fish products; if they required treatment with 5-aminosalicylates, immunosuppressives, tumor necrosis factor α antagonists, or investigational drugs; had an ostomy or short bowel syndrome; or if they had a bowel resection in the preceding 3 months or had clinically important bowel obstruction (defined by the presence of proximal dilatation demonstrated radiographically) in the 3 months prior to randomization. Patients with malignancy (with the exception of resected basal or squamous cell skin cancer or carcinoma of the cervix in situ), those with substance abuse, or those with severe medical diseases other than Crohn disease were not included.

Study Design

Eligible patients were randomly assigned, in a 1:1 ratio using a random number generator, to receive four 1-g gelatin capsules of omega-3 free fatty acids (Epanova; Tillotts Pharma AG, Ziefen, Switzerland) or 4 capsules of identical-appearing placebo each day for 52 weeks in EPIC-1 or for 58 weeks in EPIC-2. Epanova consists of 50% to 60% eicosapentanonic acid and 15% to 25% docosahexanoic acid as a free fatty acid encapsulated in a delayed-release soft gelatin capsule. The placebo capsule consisted of 1 g of medium-chain triglyceride oil. To enhance tolerability, patients began with an initial dose of 1 g/d of the study drug for the first 7 days; this was increased to 2 g/d daily for 7 days and then further increased to the final dose of 4 g/d, administered as 2 capsules twice daily.

Both studies used a central randomization procedure that was stratified by the induction therapy received prior to randomization or the duration of remission (For EPIC-1: 5-aminosalicylates; corticosteroids and in remission for 3 to 6 months; corticosteroids and in remission for 6 to 12 months; or immunosuppressives. For EPIC-2: prednisone or budesonide for induction therapy). Neither the investigators nor the patients were aware of the treatment assignment.

No new medications for Crohn disease were allowed following randomization. Participants in EPIC-2 had the dose of corticosteroid tapered. Those receiving budesonide decreased the daily dose to 3 mg by week 4, with discontinuation at week 8. Patients receiving prednisone decreased the daily dose by 2.5 mg/wk, with discontinuation at week 8. An increase in the dose of corticosteroid to control symptoms was considered a failure of treatment.

Follow-up Schedule

Patients were evaluated in the clinic at weeks –1, 0 (randomization), 4, 16, 30, 44, and 52 for EPIC-1 and at weeks –8, 0 (randomization), 2, 8, 16, 30, 44, and 58 for EPIC-2. At each visit patients were given a physical examination, blood was drawn for biochemical testing, and results of the CDAI and 36-Item Short-Form Health Survey (SF-36)[26] were assessed.

Outcome Measures

The primary efficacy outcome was the occurrence of a relapse, defined as either an increase of the CDAI score to 150 points or greater and an increase of more than 70 points from the score calculated at the randomization visit, or the initiation of prohibited medical therapy or surgery for symptomatic active Crohn disease.[4] Secondary outcomes were the change in mean scores on the CDAI and SF-36, the change in the mean serum triglyceride concentration, and the occurrence of adverse events, which were classified using the Medical Dictionary for Regulatory Activities.[27]

Adherence to the study drug as assigned was evaluated at each clinic visit by interviewing the patient and by capsule counts. Patients were considered adherent if they received at least 75% of the capsules between 2 clinic visits, with no interruption of medication for more than 14 consecutive days.

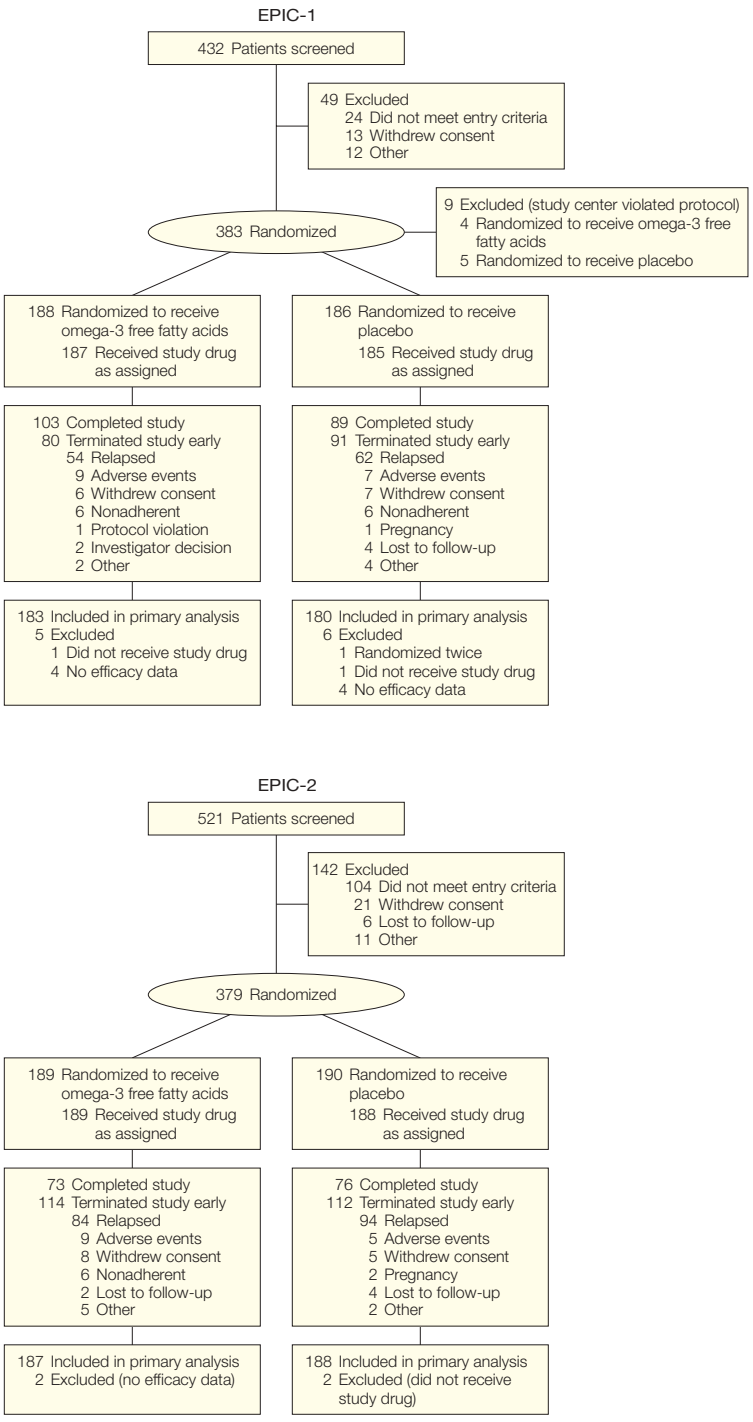
Statistical Analysis

Baseline characteristics were analyzed using the *t* test or the χ^2 test as appropriate. For the primary analysis the time to a relapse was compared by treatment group using the log-rank test. Kaplan-Meier plots were used to depict the proportion of patients remaining in remission over time. Hazard ratios (HRs) and associated confidence intervals (CIs) were obtained using Cox regression with treatment assignment as the only independent variable. For EPIC-1, a prespecified subgroup analysis was also conducted to evaluate the primary outcome in patients whose remission had been induced by corticosteroids. A Bonferroni correction ($P \leq .025$) was applied for this comparison. The mean changes in CDAI, SF-36 scores, and serum triglyceride concentrations were compared by the *t* test. Point estimates and 95% CIs of the between-group difference in the proportion of patients with adverse events were obtained. The proportion of patients compliant with the study drug was compared using the χ^2 test.

All analyses were performed according to a modified intent-to-treat principle in which data from all patients who received at least 1 dose of the study drug and who provided any postrandomization data were analyzed. A 2-sided *P* value less than .05 was considered statistically significant. SAS version 8.2[28] was used to perform these analyses; however, CIs were estimated using StatXact version 8.0.[29]

Both trials were designed to detect a 15%[30] reduction in relapse rate with 80% power at the .05 significance level. We estimated that the relapse rate in the placebo group would be 70% in EPIC-1.[21] For EPIC-2, we estimated that 80% of the patients would achieve clinical remission at the discontinuation of corticosteroid induction therapy and that the rate of relapse in the patients who were subsequently assigned to placebo would be 80%.[31] Accordingly, a total of 306 patients and 309 patients were required to detect an absolute difference of 15% in the relapse rate for EPIC-1 and EPIC-2, respectively. We planned to randomize 360 patients in EPIC-1 and 364 patients in EPIC-2 to allow for a nonevaluable rate of 15%.

Figure 1. Disposition of Patients During the Conduct of EPIC-1 and EPIC-2



EPIC indicates Epanova Program in Crohn's Study.

RESULTS

The disposition of the patients is shown in FIGURE 1. In EPIC-1, 383 patients were randomized. During the conduct of EPIC-1, it was discovered that a single site had not conducted the trial according to International Conference on Har-

monisation E6 guidelines[32] and had not followed the protocol on numerous occasions. Following consultation with regulatory agencies, all of the data collected on the 9 patients randomized from this site were excluded from analysis. Of the remaining 374 patients, 2 did not receive study drug, 8 had no postrandomization relapse assessment, and 1 was rerandomized in error. Thus, a total of 363 patients were included in the modified intent-to-treat population; of these, 183 received omega-3 free fatty acids and 180 received placebo. In EPIC-2, 379 patients were randomized, 2 did not receive study drug, and 2 had no postrandomization assessment. Thus, a total of 375 patients were included in the modified intent-to-treat population; of these, 187 received omega-3 free fatty acids and 188 received placebo.

In EPIC-1, 26 patients who did not experience relapse discontinued treatment prematurely in the omega-3 free fatty acids group compared with 29 in the placebo group ($P=.61$). In EPIC-2, 30 patients who did not experience relapse discontinued treatment prematurely in the omega-3 free fatty acids group compared with 18 in the placebo group ($P=.06$). No important differences were observed between the treatment groups in the reasons for withdrawal in either trial (Figure 1).

The baseline characteristics of the patients were similar for both treatment groups in each trial (TABLE 1).[33]

Primary Outcome

FIGURE 2 shows the proportion of patients who remained in remission over time. No significant differences were observed between the 2 treatment groups in either trial. In EPIC-1, 54 patients treated with omega-3 free fatty acids and 62 patients treated with placebo experienced a clinical relapse. The proportion of patients assigned to receive omega-3 free fatty acids who experienced a relapse within 360 days was estimated to be 31.6%, compared with 35.7% for those who received placebo (HR, 0.82; 95% CI, 0.57-1.19; $P=.30$). In EPIC-2, 84 patients treated with omega-3 free fatty acids and 94 patients treated with placebo experienced a clinical relapse. The proportion of patients assigned to receive omega-3 free fatty acids who experienced a relapse within 360 days was estimated to be 47.8%, compared with 48.8% of those who received placebo (HR, 0.90; 95% CI, 0.67-1.21; $P=.48$).

Table 1. Baseline Characteristics of the Study Patients in EPIC-1 and EPIC-2[a]

	EPIC-1			EPIC-2		
Characteristic	Omega-3 Free Fatty Acids (n = 183)	Placebo (n = 180)	*P* Value	Omega-3 Free Fatty Acids (n = 187)	Placebo (n = 188)	*P* Value
Characteristic						
Age, mean (SD), y	40.5 (15.2)	38.2 (13.1)	.12	38.5 (13.8)	40.0 (13.6)	.28
Male sex, No. (%)	88 (48.1)	74 (41.1)	.18	81 (43.3)	79 (42.0)	.80
Weight, mean (SD), kg	69.0 (13.2)	67.9 (13.8)	.42	69.8 (15.5)	68.4 (16.1)	.40
Current smoker, No. (%)	56 (30.6)	62 (34.4)	.43	47 (25.1)	70 (37.2)	.01
Remission induction therapy, No. (%)						
Oral 5-ASA or antibiotics	82 (44.8)	83 (46.1)	.97			
Steroids, in remission 3-6 mo	57 (31.1)	57 (31.7)				
Steroids, in remission >6-12 mo	36 (19.7)	32 (17.8)				
Immunosuppressives	8 (4.4)	8 (4.4)				
Prednisone				106 (56.7)	110 (58.5)	.72
Budesonide				81 (43.3)	78 (41.5)	
Harvey-Bradshaw index, mean (SD)[b]	2.3 (2.0)	2.3 (2.3)	.82	6.2 (4.2)	6.0 (3.6)	.58
Crohn's Disease Activity Index, mean (SD)[c]	79.6 (40.7)	75.4 (43.5)	.34	77.4 (44.8)	78.0 (41.6)	.90
Months since diagnosis						
Mean (SD)	85.7 (106.3)	82.7 (98.9)	.78	84.6 (94.0)	90.6 (108.5)	.57
Median (range)	42.0 (4-540)	42.5 (1-465)		51.0 (1-427)	42.0 (2-482)	
Previous surgery for Crohn disease, No. (%)	61 (33.3)	64 (35.6)	.66	56 (29.9)	67 (35.6)	.24
Crohn disease therapy prior 12 mo, No. (%)						
Oral 5-ASA therapy	142 (77.6)	141 (78.3)	.87	102 (54.5)	90 (47.9)	.20
Topical rectal therapy	9 (4.9)	8 (4.4)	.83	5 (2.7)	11 (5.9)	.13
Systemic corticosteroids	97 (53.0)	94 (52.2)	.88	39 (20.9)	36 (19.1)	.68
Immune-modifying agents	12 (6.6)	15 (8.3)	.52	13 (7.0)	13 (6.9)	.99
Immune modifiers/biologics	3 (1.6)	2 (1.1)	.67	4 (2.1)	3 (1.6)	.70
Antibiotic therapy	37 (20.2)	32 (17.8)	.55	23 (12.3)	25 (13.3)	.77

Abbreviations: ASA, aminosalicylate; EPIC, Epanova Program in Crohn's Study.
[a] Values for comparison of continuous outcomes were derived by the *t* test. Pearson χ^2 test was used to compare categorical variables.
[b] Harvey-Bradshaw scores range from 0 to approximately 14. Higher scores indicate worse disease activity; scores of ≤4 are associated with clinical remission. Baseline score for EPIC=2 was assessed at the screening visit prior to steroid tapering.
[c] Scores of ≤150 points are associated with quiescent disease, scores >150 points indicate active disease, and scores >450 points are seen with extremely severe disease.

In the subgroup of patients in EPIC-1 who had received induction therapy with corticosteroids, no significant difference was observed between the 2 treatment groups. Thirty-eight percent of those who received omega-3 free fatty acids experienced a relapse at 360 days compared with 39.5% in the placebo group ($P=.60$).

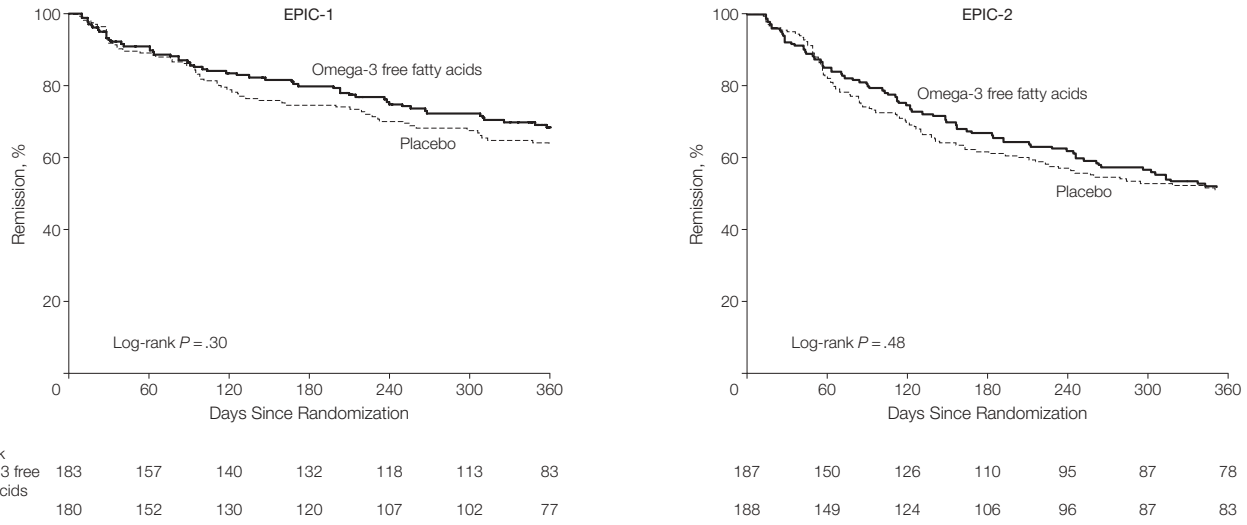
Disease Activity and Quality of Life

No important differences were observed in the changes in mean CDAI and SF-36 scores in either study (data not shown).

Adherence to Study Drug

In EPIC-1, 79.2% of patients who received omega-3 free fatty acids had adequate adherence to study drug, compared with 75.6% of those who received placebo ($P=.40$). The corresponding values for EPIC-2

Figure 2. Kaplan-Meier Estimates of the Time to Relapse in the Omega-3 Free Fatty Acids and Placebo Groups for EPIC-1 and EPIC-2



EPIC indicates Epanova Program in Crohn's Study.

Table 2. Incidence of Adverse Events, EPIC-1 and EPIC-2[a]

	No. (%)					
	EPIC-1			EPIC-2		
Adverse Event	Omega-3 Free Fatty Acids (n = 187)	Placebo (n = 184)	Difference (95% CI)[b]	Omega-3 Free Fatty Acids (n = 189)	Placebo (n = 188)	Difference (95% CI)[b]
Crohn disease worsening	47 (25.1)	57 (31.0)	–5.8 (–14.9 to 3.3)	78 (41.3)	89 (47.3)	–6.1 (–16.0 to 4.0)
Abdominal pain	45 (24.1)	41 (22.3)	1.8 (–6.8 to 10.4)	65 (34.4)	62 (33.0)	1.4 (–8.1 to 10.9)
Diarrhea	35 (18.7)	21 (11.4)	7.3 (0 to 14.7)	44 (23.3)	37 (19.7)	3.6 (–4.7 to 11.9)
Arthralgia	21 (11.2)	15 (8.2)	3.1 (–3.1 to 9.3)	29 (15.3)	28 (14.9)	0.5 (–6.9 to 7.8)
Nasopharyngitis	18 (9.6)	13 (7.1)	2.6 (–3.2 to 8.5)	29 (15.3)	27 (14.4)	1.0 (–6.3 to 8.3)
Nausea	17 (9.1)	4 (2.2)	6.9 (2.4 to 12.2)	30 (15.9)	19 (10.1)	5.8 (–1.0 to 12.7)
Headache	12 (6.4)	10 (5.4)	1.0 (–4.1 to 6.1)	12 (6.3)	20 (10.6)	–4.3 (–10.2 to 1.4)
Influenza	12 (6.4)	14 (7.6)	–1.2 (–6.7 to 4.2)	6 (3.2)	7 (3.7)	–0.5 (–4.7 to 3.5)
Flatulence	11 (5.9)	13 (7.1)	–1.2 (–6.5 to 4.0)	12 (6.3)	12 (6.4)	6.3 (–5.2 to 5.2)
Gastroenteritis	10 (5.3)	10 (5.4)	–0.1 (–5.0 to 4.8)	6 (3.2)	8 (4.3)	–1.1 (–5.4 to 3.0)
Fatigue	10 (5.3)	6 (3.3)	2.1 (–2.3 to 6.7)	22 (11.6)	22 (11.7)	–0.1 (–6.7 to 6.6)
Dysgeusia	2 (1.1)	1 (0.5)	0.5 (–2.0 to 3.3)	10 (5.3)	2 (1.1)	4.2 (0.8 to 8.5)
Dyspepsia	4 (2.1)	5 (2.7)	–0.6 (–4.3 to 3.0)	14 (7.4)	13 (6.9)	–0.5 (–4.9 to 6.0)
Hematochezia	0	2 (1.1)	–1.1 (–3.9 to 0.9)	9 (4.8)	10 (5.3)	–0.6 (–5.3 to 4.2)
Sinusitis	1 (0.5)	3 (1.6)	–1.1 (–4.2 to 1.5)	3 (1.6)	15 (8.0)	–6.4 (–11.4 to –2.3)
Vomiting	4 (2.1)	2 (1.1)	1.1 (–2.0 to 4.4)	13 (6.9)	11 (5.9)	1.0 (–4.1 to 6.3)

Abbreviations: CI, confidence interval; EPIC, Epanova Program in Crohn's Study.
[a] Table shows the proportion of patients experiencing adverse events by more than 5% of the patients in any treatment group in EPIC-1 or EPIC-2. Seven pregnancies occurred during the trials; 2 occurred in patients who received omega-3 free fatty acids and 5 in those who received placebo.
[b] 95% CIs obtained using inversion of 2-sided χ^2 tests.

were 75.4% and 81.4%, respectively ($P=.16$).

Serum Triglycerides

A significant decrease in serum triglyceride concentration was observed in patients assigned to receive omega-3 free fatty acids. In EPIC-1, the mean decrease after 30 weeks of treatment was –21.5 mg/dL (to convert to millimoles per liter, multiply by 0.0113), compared with a mean increase of 16.5 mg/dL in patients who received placebo ($P<.001$). Corresponding values for EPIC-2 were –27.1 mg/dL in patients treated with omega-3 free fatty acids, compared with –5.1 mg/dL in patients receiving placebo ($P=.02$).

Adverse Events

No important differences were observed between the treatment groups in the incidence of adverse events (TABLE 2). The overall frequency of adverse events was higher in EPIC-2 because these patients had active disease at the time of entry and were receiving treatment with corticosteroids. The omega-3 free fatty acid formulation was well tolerated, and previously observed adverse events such as diarrhea and bloating[21] were uncommon. No differences in laboratory results were identified apart from the reduced triglyceride concentration observed in patients who received omega-3 free fatty acids.

COMMENT

These 2 large-scale trials had similar results. No beneficial effect of high-dose omega-3 free fatty acid treatment was observed for the prevention of relapse over 1 year of follow-up. These findings are distinctly different from those of Belluzzi at al,[21] who reported a 33% absolute reduction in the rate of relapse following treatment with a similar omega-3 free fatty acid formulation in a randomized placebo-controlled trial that evaluated 78 patients.

There are 3 possible explanations for these discordant results. First, the design of the study by Belluzzi et al[21] differed from the EPIC trials in that only patients at a high risk of relapse, defined by the presence of an elevated serum concentration of acute-phase reactants, were included. It could be speculated that the patients evaluated in the EPIC studies were at such low risk that the trials lacked sufficient statistical power to detect the prespecified 15% benefit of treatment. While this hypothesis might be plausible in the case of EPIC-1, given that the 1-year placebo relapse rate was only 35.7%, it is not tenable for EPIC-2, in which 51.2% of patients relapsed. Furthermore, our results are consistent with those of Lorenz-Meyer et al,[22] who also demonstrated no benefit of omega-3 fatty acids in a placebo-controlled relapse prevention study that evaluated 204 patients.

A second possible explanation concerns the different formulations used in the studies. The formulation evaluated in the study by Belluzzi et al was a hard gelatin capsule, in contrast to the soft gelatin capsule used in the current trials. However, pharmacokinetic studies have shown that a similar concentration of omega-3 free fatty acids is incorporated into cell membranes following administration of either preparation (J.S., written communication, January 2004, data on file). Moreover, although no beneficial effect was observed for the prevention of relapse, a statistically significant decrease in the serum concentration of triglycerides was observed in patients who received omega-3 free fatty acids. This finding, which is consistent with our analysis of the capsule counts, indicates the patients had adequate exposure to the study drug and that poor compliance cannot account for the negative results.

Finally, we believe that the most plausible explanation for the discordant findings is that the study by Belluzzi et al, which only evaluated 78 patients, was incorrect in concluding that treatment with omega-3 free fatty acids is beneficial. Several studies have demonstrated that small clinical trials are more susceptible to bias, are often less methodologically rigorous, and produce relatively less precise estimates of the true effect of treatment than large, multicenter studies.[34-36]

Our results are important because the use of alternative medicines in general, and omega-3 free fatty acid formulations in particular, is widespread among patients with inflammatory bowel disease.[37-41] This may be due, in part, to dissemination of the positive results obtained in the trial by Belluzzi et al. Given the negative results observed in the EPIC trials and in the trial by Lorenz-Meyer et al,[22] we do not endorse this practice, since patients with Crohn disease who are at risk for relapse would be better served by taking medications of known efficacy.

The omega-3 free fatty acid formulation was well tolerated. In contrast to the results obtained in the study by Belluzzi et al,[21] during the first month of treatment only 2.7% of patients had to discontinue the drug due to diarrhea. The increased tolerability was likely due to the gradual increase in dosing specified by the protocols. Although a theoretical risk of bleeding due to platelet dysfunction exists with omega-3 free fatty acid treatment,[42,43] no serious bleeding problems were encountered despite the administration of a relatively high drug dose.

In summary, in the EPIC-1 and EPIC-2 trials administration of a high dose of omega-3 free fatty acids did not reduce the rate of relapse in patients with quiescent Crohn disease.

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Author Contributions: Dr Feagan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Drafting of the manuscript: Feagan, Hébuterne, Klvana, Ardizzone, Kiudelis.

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