

# The New England Journal of Medicine

©Copyright, 1996, by the Massachusetts Medical Society

Volume 334

JUNE 13, 1996

Number 24

## EFFECT OF AN ENTERIC-COATED FISH-OIL PREPARATION ON RELAPSES IN CROHN'S DISEASE

ANDREA BELLUZZI, M.D., CORRADO BRIGNOLA, M.D., MASSIMO CAMPIERI, M.D., ANGELO PERA, M.D.,  
STEFANO BOSCHI, M.S., AND MARIO MIGLIOLI, M.D.

**Abstract Background.** Patients with Crohn's disease may have periods of remission, interrupted by relapses. Because fish oil has antiinflammatory actions, it could reduce the frequency of relapses, but it is often poorly tolerated because of its unpleasant taste and gastrointestinal side effects.

**Methods.** We performed a one-year, double-blind, placebo-controlled study to investigate the effects of a new fish-oil preparation in the maintenance of remission in 78 patients with Crohn's disease who had a high risk of relapse. The patients received either nine fish-oil capsules containing a total of 2.7 g of n-3 fatty acids or nine placebo capsules daily. A special coating protected the capsules against gastric acidity for at least 30 minutes.

**Results.** Among the 39 patients in the fish-oil group, 11 (28 percent) had relapses, 4 dropped out because of diarrhea, and 1 withdrew for other reasons. In contrast, among

the 39 patients in the placebo group, 27 (69 percent) had relapses, 1 dropped out because of diarrhea, and 1 withdrew for other reasons (difference in relapse rate, 41 percentage points; 95 percent confidence interval, 21 to 61;  $P < 0.001$ ). After one year, 23 patients (59 percent) in the fish-oil group remained in remission, as compared with 10 (26 percent) in the placebo group ( $P = 0.003$ ). Logistic-regression analysis indicated that only fish oil and not sex, age, previous surgery, duration of disease, or smoking status affected the likelihood of relapse (odds ratio for the placebo group as compared with the fish-oil group, 4.2; 95 percent confidence interval, 1.6 to 10.7).

**Conclusions.** In patients with Crohn's disease in remission, a novel enteric-coated fish-oil preparation is effective in reducing the rate of relapse. (N Engl J Med 1996; 334:1557-60.)

©1996, Massachusetts Medical Society.

CROHN'S disease is characterized by remission and relapse. The relapses are most likely to occur soon after patients enter remission and are more frequent in those with abnormalities in serum concentrations of acute-phase proteins.<sup>1-3</sup> Because fish oil has antiinflammatory actions, its use has been proposed in patients with several inflammatory diseases, including inflammatory bowel disease.<sup>4-8</sup> However, its unpleasant taste and its side effects, which include flatulence, heartburn, halitosis, belching, and diarrhea, make it unacceptable to many patients.<sup>9-11</sup>

We have found that the rate of absorption of the component n-3 fatty acids in fish oil is high when they are administered in the form of a new, enteric-coated preparation, so that the dose needed to achieve the incorporation of fish-oil fatty acids into phospholipid membranes is one third of that used previously.<sup>12</sup> As a result, the frequency of side effects is reduced, compliance in-

creases, and long-term treatment becomes feasible for many patients.

In this study, we investigated the effects of the new, enteric-coated fish-oil preparation in the maintenance of remission in patients with Crohn's disease.

### METHODS

Between May 1992 and September 1993, patients treated in our outpatient clinic who had an established diagnosis of Crohn's disease and were in clinical remission were evaluated for eligibility for this study with use of the Crohn's Disease Activity Index.<sup>13</sup> This index incorporates eight items — the daily number of liquid or very soft stools, abdominal pain, general well-being, extraintestinal manifestations of Crohn's disease, use of opiates to treat diarrhea, abdominal mass, hematocrit, and body weight — to yield a composite score ranging from 0 to 600. Higher scores indicate more disease activity. Patients with scores of 150 or less are considered to have inactive disease. The criterion for eligibility for our study was a score that had been below 150 for at least three months but less than two years.

In addition to having a score below 150 on this index, the patients had to have at least one of the following: a serum  $\alpha_1$ -acid glycoprotein concentration above 130 mg per deciliter (normal reference range,  $<120$  mg per deciliter), a serum  $\alpha_2$ -globulin concentration above 0.9 g per deciliter (normal reference range,  $<0.8$  g per deciliter), or an erythrocyte sedimentation rate of more than 40 mm per hour (normal reference range,  $<20$  mm per hour). Patients were excluded if they were less than 18 or more than 75 years old, had received mesalamine, sulfasalazine, or corticosteroids in the previous

From the Institute of Clinical Medicine and Gastroenterology (A.B., C.B., M.C., M.M.) and the Department of Clinical Pharmacology (S.B.), University of Bologna, Bologna; and the Department of Gastroenterology, S. Giovanni Battista Hospital, Turin (A.P.) — both in Italy. Address reprint requests to Dr. Belluzzi at Via Vizzani, 36, 40138 Bologna, Italy.

Supported by Tillotts Pharma, Ziefen, Switzerland.

three months or immunosuppressive drugs in the previous six months, or had undergone resection of more than 1 m of bowel in the past; patients who had undergone less extensive resection were eligible only if they had had clinical and endoscopic or radiologic evidence of recurrence after surgery, with subsequent remission.

Of 89 potentially eligible patients, 78 were enrolled in the one-year study. The reasons for exclusion were a decision by the patient not to participate in the study (five patients), pregnancy or a desire to become pregnant (three patients), and inability to keep follow-up appointments (three patients).

The patients were randomly assigned to receive either three enteric-coated capsules of fish oil three times daily (Purepa, Tillotts Pharma, Ziefen, Switzerland) or three enteric-coated capsules of identical appearance containing 500 mg of placebo three times daily. The placebo used was Miglyol 812 (Dynamit Nobel Chemicals, Witten, Germany), a mixed-acid triglyceride of fractionated fatty acids made up of 60 percent caprylic acid and 40 percent capric acid. The fish-oil capsules each contained 500 mg of a new marine lipid concentrate in free-fatty-acid form (40 percent eicosapentaenoic acid and 20 percent docosahexaenoic acid; the remaining 40 percent was a mixture of n-7 fatty acids [17 percent], n-9 fatty acids [16 percent], and n-6 fatty acids [7 percent]), resulting in daily doses of 1.8 g of eicosapentaenoic acid and 0.9 g of docosahexaenoic acid.

The capsules were specially coated (Eudragit NE 30D, Röhm, Darmstadt, Germany) to resist gastric acid for at least 30 minutes but to disintegrate within 60 minutes, thus allowing the release of fish oil into the small intestine. The study medications were packed identically and labeled with each patient's code number according to a balanced-block randomization scheme. There was no difference in odor between the fish-oil and placebo preparations, provided the capsules were not broken. During treatment the patients took no other medication.

All the patients were examined by two physicians on entry into the study and at 3, 6, 9, and 12 months, or earlier if their symptoms worsened. Relapse was defined as an increase in the score on the Crohn's Disease Activity Index to at least 100 points more than the base-line value and a score above 150 for more than two weeks. Compliance was assessed by pill counts. At each visit, routine laboratory tests were performed, including a blood count; measurement of the erythrocyte sedimentation rate and serum creatinine,  $\alpha$ 1-acid glycoprotein, and  $\alpha$ 2-globulins; and liver-function tests. Before and at the end of the study, 2 ml of packed red cells was obtained for the determination of

Table 1. Base-Line Characteristics of 78 Patients with Crohn's Disease in Remission.

CHARACTERISTIC	PLACEBO (N = 39)	FISH OIL (N = 39)
Age (yr)		
Median	39	34
Range	20-65	18-67
Sex (M/F)	19/20	20/19
Cigarette smokers (no.)	13	14
Duration of disease (mo)		
Median	66	68
Range	20-88	24-94
Previous resection (no. of patients)	13	14
Duration of remission (mo)		
Median	7	8
Range	3-23	3-23
Drugs used to obtain last remission (no. of patients)		
Immunosuppressive agents	0	0
Corticosteroids	22	19
Mesalamine	17	20
Site of involvement (no. of patients)		
Ileum	20	20
Ileum and colon	15	14
Colon	4	5
Score on Crohn's Disease Activity Index		
Median	82	78
Range	30-112	28-120

Table 2. Clinical Results during Treatment with Fish Oil or Placebo in Patients with Crohn's Disease in Remission.

VARIABLE	PLACEBO	FISH OIL
	no. (%)	
<b>Outcome*</b>		
Total no. of patients	39	39
Lost to follow-up	1 (3)	1 (3)
Withdrew because of diarrhea	1 (3)	4 (10)
Remained in remission	10 (26)	23 (59)
Relapse	27 (69)	11 (28)
<b>Major symptoms in patients with relapse</b>		
Total no. of patients	27	11
Diarrhea (>4 liquid stools/day)	23 (85)	10 (91)
Moderate or severe abdominal pain	25 (93)	10 (91)
Fever (temperature, >37.7°C)	12 (44)	3 (27)
General condition poor or very poor	27 (100)	11 (100)
Arthritis	14 (52)	6 (55)

\*Because of rounding, percentages do not total 100 for the placebo group.

the fatty-acid phospholipid profile of the cells by gas chromatography, as previously described.<sup>12</sup>

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committee of the University of Bologna and the clinical boards of the hospitals; all the patients gave informed consent.

### Statistical Analysis

The differences in the rates of relapse and the proportions of patients remaining in remission in the fish-oil and placebo groups were analyzed with the chi-square test. Differences between the groups in clinical findings and changes in laboratory results during the study were analyzed with the Mann-Whitney U test. Kaplan-Meier life-table curves were calculated for patients remaining in remission who were assigned to the two treatments.<sup>14</sup> Differences in the curves were tested by log-rank analysis. Multivariate logistic-regression analysis was performed with treatment, sex, age, previous surgery, duration of disease, and smoking status as independent variables and with clinical relapse as the outcome variable.<sup>15</sup> SOLO-BMDP Statistical Software (version 3.0, BMDP, Los Angeles) was used for statistical analysis. All statistical tests were two-tailed.

## RESULTS

The characteristics of the 78 patients are shown in Table 1. There were no significant differences between the groups at base line. Among the 39 patients in the fish-oil group 11 (28 percent) had relapses, 1 patient moved away, and 4 dropped out because of diarrhea. Among the 39 patients in the placebo group, 27 (69 percent) had relapses, 1 patient moved away, and 1 dropped out because of diarrhea (difference in relapse rates, 41 percentage points; 95 percent confidence interval, 21 to 61;  $P < 0.001$ ) (Table 2). In all five patients who had diarrhea, symptoms began within the first month of treatment and did not improve when the daily intake of capsules was reduced. There were no other side effects. The distribution of disease in the intestines of the patients who had relapses was similar to that in the group as a whole at base line. All patients who had relapses were treated with 0.75 to 1 mg of methylprednisolone per kilogram of body weight daily for at least three weeks.

After one year of treatment, 23 of the 39 patients in the fish-oil group (59 percent) were still in remission,

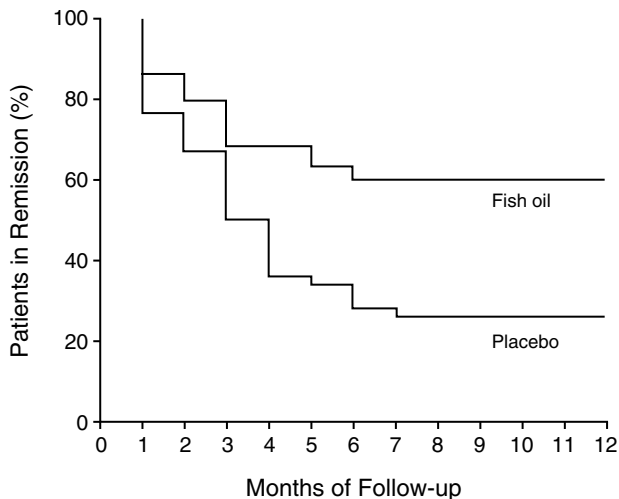


Figure 1. Life-Table Curves Showing the Percentage of All Randomized Patients Who Remained in Clinical Remission during the One-Year Treatment Period.

There were 39 patients in each group.  $P=0.006$  for the comparison of the two groups by log-rank analysis.

as compared with only 10 of the 39 patients in the placebo group (26 percent,  $P=0.003$ ). Figure 1 shows the Kaplan-Meier life-table curves for patients remaining in clinical remission ( $P=0.006$  by log-rank analysis). The multivariate logistic-regression analysis indicated that only fish-oil treatment affected the likelihood of relapse (odds ratio for relapse in the placebo group vs. the fish-oil group, 4.2; 95 percent confidence interval, 1.6 to 10.7); sex, age, previous surgery, duration of disease, and smoking status were not significant determinants of relapse.

With regard to the laboratory tests for indicators of inflammation, there was a significant decrease in all such markers in the fish-oil group as compared with the placebo group at the end of the study (Table 3). The analysis of the main fatty acids in red cells from the patients who were still in remission at the end of the study indicated the incorporation of n-3 fatty acids into the phospholipid membranes of patients given fish oil, displacing arachidonic acid almost completely (Table 4).

## DISCUSSION

Fish oil has been suggested as a treatment for a variety of chronic inflammatory disorders. Its antiinflammatory effect may be due to reduced production of leukotriene  $B_4$  and thromboxane  $A_2$ ,<sup>16</sup> which are elevated in the inflamed intestinal mucosa of patients with Crohn's disease,<sup>17</sup> or inhibition of the synthesis of cytokines such as interleukin- $1\beta$  and tumor necrosis factor.<sup>18</sup> It can also scavenge free radicals.<sup>19</sup>

In addition to inflammation, multifocal gastrointestinal infarction has been suggested as an early pathogenic event in Crohn's disease<sup>20</sup>; its presence may indicate a pivotal role in the pathogenesis of platelets and possibly thromboxane  $A_2$ , a powerful platelet-aggregating agent.<sup>21</sup> The capacity of fish oil to inhibit<sup>22</sup> the production of thromboxane  $A_2$  could be relevant to the treat-

ment of Crohn's disease, since treatment with n-3 fatty acids decreases platelet responsiveness in patients with this disorder.<sup>23</sup> Fish oil may also induce enterocyte hyperplasia, thereby increasing the mucosal surface area, with a corresponding increase in enteral absorption of nutrients and improvement of nutrition.<sup>24</sup>

There have been only two reported trials of fish oil in patients with Crohn's disease. Matè et al.<sup>7</sup> reported that remissions were more prolonged in patients who received a diet rich in fish oil for two years. By contrast, Lorenz et al.<sup>8</sup> found that 1.8 g of eicosapentaenoic acid daily did not affect the clinical activity of the disease. In our study, the patients receiving the fish-oil formula were significantly less likely to have relapses than the patients receiving placebo. The patients had been in clinical remission for less than 24 months before the study, and all had some laboratory evidence of inflammation. Patients with these characteristics have about a 75 percent greater risk of relapse than those who have been in remission longer and have normal laboratory-test results.<sup>25</sup>

The coated fish-oil preparation we used has few gastric side effects, and patients' level of compliance was high. Furthermore, the degree of absorption of the n-3 free fatty acids and of their incorporation into phospholipid membranes was high (Table 4); with other fish-oil preparations, in contrast, triglycerides and ethyl esters require lipase activity for absorption.<sup>12,26,27</sup>

Ten percent of the patients in the fish-oil group dropped out because they had diarrhea. This may have been due to the slower breakdown of the capsules and the resulting delivery of the contents to the distal part of the gut. Disintegration of the coating requires 30 to 60 minutes; therefore, if the transit time is short, the capsules would remain intact further along the intestine.

In several trials, treatment with mesalamine decreased the frequency of clinical relapse in patients with Crohn's disease.<sup>3,28-30</sup> In these trials, mesalamine reduced the rate of relapse by 25 to 30 percent, as compared with placebo.<sup>31</sup> In most of the trials, the rate of relapse in the placebo group ranged from 25 to 55 percent at 12

Table 3. Changes in Laboratory-Test Results during the Study, According to Group Assignment.\*

INDEX	PLACEBO (N = 39)	FISH OIL (N = 39)
Erythrocyte sedimentation rate		
Base line — mm/hr	35±4	36±4
End of study — mm/hr	42±4.6	28±3.5
Change — % (95% CI)	+14 (2 to 26)	-20 (-6 to -34)†
Serum $\alpha_2$ -globulins		
Base line — g/dl	0.92±0.02	0.96±0.03
End of study — g/dl	1.05±0.04	0.85±0.02
Change — % (95% CI)	+15 (3 to 27)	-9 (-18 to 0)†
Serum $\alpha_1$ -acid glycoprotein		
Base line — mg/dl	137±8.7	136±8.5
End of study — mg/dl	159±10	130±9.4
Change — % (95% CI)	+17 (10 to 24)	-4 (-10 to 2)‡

\*Plus-minus values are means  $\pm$  SE. CI denotes confidence interval. The normal reference ranges are as follows: erythrocyte sedimentation rate, <20 mm per hour; serum  $\alpha_2$ -globulins, <0.8 g per deciliter; serum  $\alpha_1$ -acid glycoprotein, <120 mg per deciliter.

† $P<0.001$  for the comparison of the changes in the two groups.

‡ $P=0.02$  for the comparison of the changes in the two groups.

**Table 4. Changes in the Levels of Major Fatty Acids in Red Cells from Patients Remaining in Remission at the End of the Study, According to Group Assignment.\***

ACID	PLACEBO (N = 10)	FISH OIL (N = 23)
Linoleic acid (C18:2, n-6)		
Base line — %	10.6±0.5	10.2±0.5
End of study — %	11.1±0.5	6.4±0.1
Change — % (95% CI)	+1 (-2.1 to 3.9)	-40 (-14 to -65)†
Arachidonic acid (C20:4, n-6)		
Base line — %	13.5±0.4	13.9±0.3
End of study — %	14.1±0.3	7.1±0.2
Change — % (95% CI)	+0.5 (-3.4 to 4)	-48 (-20 to -76)†
Eicosapentaenoic acid (C20:5, n-3)		
Base line — %	0.3±0.03	0.2±0.02
End of study — %	0.2±0.03	5.8±0.1
Change — % (95% CI)	-3 (-13 to 7)	+2800 (2632 to 3068)†
Docosahexaenoic acid (C22:6, n-3)		
Base line — %	3.2±0.1	2.9±0.1
End of study — %	3±0.2	11.4±0.2
Change — % (95% CI)	-7 (-23 to 9)	+360 (287 to 443)†

\*Plus-minus values are means ±SE. Fatty-acid levels are expressed as relative percentages of total fatty acids. CI denotes confidence interval.

†P<0.001 for the comparison of the changes in the two groups.

months, but these percentages are not comparable to that in our study because of differences in the characteristics of the patients. In a study of patients similar to ours, the relapse rate was 83 percent in the placebo group and 62 percent in the mesalamine group after 12 months.<sup>29</sup>

Our results indicate that the new coated fish-oil preparation is an effective, well-tolerated treatment that prevents clinical relapses in patients with Crohn's disease in remission. Its efficacy in relation to that of mesalamine, currently the standard treatment for the maintenance of remission in patients with Crohn's disease, remains to be determined.

We are indebted to Marco Astegiano, M.D., Fernando Rizzello, M.D., Alessandra Munarini, B.D., Clarissa Belloli, M.D., Giuliana De Simone, M.D., Loris Pironi, M.D., and Roberta Roberti, M.D., for their continuous support of our research and to Professor Lloyd Sutherland, Professor Alan Bennett, and Dr. Claudio Borghi for their helpful comments.

## REFERENCES

- Wright JP, Young GO, Tigler-Wybrandi N. Predictors of acute relapse of Crohn's disease: a laboratory and clinical study. *Dig Dis Sci* 1987;32:164-70.
- Brignola C, Campieri M, Bazzocchi G, Farruggia P, Tragnone A, Lanfranchi GA. A laboratory index for predicting relapse in asymptomatic patients with Crohn's disease. *Gastroenterology* 1986;91:1490-4.
- Gendre JP, Mary JY, Florent C, et al. Oral mesalamine (Pentasa) as maintenance treatment in Crohn's disease: a multicenter placebo-controlled study. *Gastroenterology* 1993;104:435-9.
- Hawthorne AB, Daneshmend TK, Hawkey CJ, et al. Treatment of ulcerative colitis with fish oil supplementation: a prospective 12 month randomised controlled trial. *Gut* 1992;33:922-8.
- Stenson WF, Cort D, Rodgers J, et al. Dietary supplementation with fish oil in ulcerative colitis. *Ann Intern Med* 1992;116:609-14.
- Aslan A, Triadafilopoulos G. Fish oil fatty acid supplementation in active ulcerative colitis: a double-blind, placebo-controlled, crossover study. *Am J Gastroenterol* 1992;87:432-7.
- Matè J, Castaños R, García-Samaniego J, Pajares JM. Does dietary fish oil maintain the remission of Crohn's disease (CD): a study case control. *Gastroenterology* 1991;100:Suppl:A228. abstract.
- Lorenz R, Weber PC, Szimnau P, Heldwein W, Strasser T, Loeschke K. Supplementation with n-3 fatty acids from fish oil in chronic inflammatory bowel disease — a randomized, placebo-controlled, double-blind cross-over trial. *J Intern Med Suppl* 1989;225:225-32.
- Appel LJ, Miller ER III, Seidler AJ, Whelton PK. Does supplementation of diet with "fish oil" reduce blood pressure? A meta-analysis of controlled clinical trials. *Arch Intern Med* 1993;153:1429-38.
- O'Connor GT, Malenka DJ, Olmstead EM, Johnson PS, Hennekens CH. A meta-analysis of randomized trials of fish oil in prevention of restenosis following coronary angioplasty. *Am J Prev Med* 1992;8:186-92.
- Donnelly SM, Ali MA, Churchill DN. Effect of n-3 fatty acids from fish oil on hemostasis, blood pressure, and lipid profile of dialysis patients. *J Am Soc Nephrol* 1992;2:1634-9.
- Belluzzi A, Brignola C, Campieri M, et al. Effects of new fish oil derivative on fatty acid phospholipid-membrane pattern in a group of Crohn's disease patients. *Dig Dis Sci* 1994;39:2589-94.
- Best WR, Beckett JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index: National Cooperative Crohn's Disease Study. *Gastroenterology* 1976;70:439-44.
- Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-81.
- Hosmer DW Jr, Lemeshow S. *Applied logistic regression*. New York: John Wiley, 1989.
- Lee TH, Hoover RL, Williams JD, et al. Effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene generation and neutrophil function. *N Engl J Med* 1985;312:1217-24.
- Rampton DS, Collins CE. Thromboxanes in inflammatory bowel disease — pathogenic and therapeutic implications. *Aliment Pharmacol Ther* 1993;7:357-67.
- Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N Engl J Med* 1989;320:265-71.
- Fisher M, Upchurch KS, Levine PH, et al. Effects of dietary fish oil supplementation on polymorphonuclear leucocyte inflammatory potential. *Inflammation* 1986;10:387-92.
- Wakefield AJ, Sawyerr AM, Dhillon AP, et al. Pathogenesis of Crohn's disease: multifocal gastrointestinal infarction. *Lancet* 1989;2:1057-62.
- Webberley MJ, Hart MT, Melikian V. Thromboembolism in inflammatory bowel disease: role of platelets. *Gut* 1993;34:247-51.
- MacIntyre DE, Hoover RL, Smith M, et al. Inhibition of platelet function by cis-unsaturated fatty acids. *Blood* 1984;63:848-57.
- Jaschonek K, Clemens MR, Scheurlen M. Decreased responsiveness of platelets to a stable prostacyclin analogue in patients with Crohn's disease: reversal by n-3 polyunsaturated fatty acids. *Thromb Res* 1991;63:667-72.
- Vanderhoof JA, Park JHY, Herrington MK, Adrian TE. Effects of dietary menhaden oil mucosal adaptation after small bowel resection in rats. *Gastroenterology* 1994;106:94-9.
- Brignola C, Iannone P, Belloli C, et al. Prediction of relapse in patients with Crohn's disease in remission: a simplified index using laboratory tests, enhanced by clinical characteristics. *Eur J Gastroenterol Hepatol* 1994;6:955-61.
- el Boustani S, Colette C, Monnier L, Descamps B, de Paulel AC, Mendy F. Enteral absorption in man of eicosapentaenoic acid in different chemical forms. *Lipids* 1987;22:711-4.
- Lawson LD, Hughes BG. Human absorption of fish oil fatty acids as triacylglycerols, free acids, or ethyl esters. *Biochem Biophys Res Commun* 1988;152:328-35.
- International Mesalazine Study Group. Coated oral 5-aminosalicylic acid versus placebo in maintaining remission of inactive Crohn's disease. *Aliment Pharmacol Ther* 1990;4:55-64.
- Prantera C, Pallone F, Brunetti G, Cottone M, Miglioli M, Italian IBD Study Group. Oral 5-aminosalicylic acid (Asacol) in the maintenance treatment of Crohn's disease. *Gastroenterology* 1992;103:363-8.
- Brignola C, Iannone P, Pasquali S, et al. Placebo-controlled trial of oral 5-ASA in relapse prevention of Crohn's disease. *Dig Dis Sci* 1992;37:29-32.
- Messori A, Brignola C, Trallori G, et al. Effectiveness of 5-aminosalicylic acid for maintaining remission in patients with Crohn's disease: a meta-analysis. *Am J Gastroenterol* 1994;89:692-8.