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n-3 Fatty acids for the treatment of inflammatory bowel diseases

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The aim of the present paper is to briefly review the literature relating to clinical studies of the use of polyunsaturated long-chain fatty acids in the treatment of inflammatory bowel diseases (IBD) such as ulcerative colitis and Crohn's disease. The reasons for the discrepancies in the findings could be related to the different study designs, different treatments, overlapping of treatment effects, as well as the variety of treatment formulations and doses used, which have led to results that are, in certain instances, very difficult to explain. Emphasis on a treatment formulation which reduces the incidence of side effects, together with careful selection of patients and experimental design, seems to be associated with benefits, and these studies point to the therapeutic potential for these lipids in the therapy of IBD. It is possible that these fatty acids act by reducing low-grade active inflammation rather than by preventing reinitiation of the inflammatory process from a truly quiescent state. Whether this treatment is applicable to all IBD patients has not been fully elucidated. Nevertheless, taken together, all these studies suggest the effectiveness of these new therapeutic approaches, not only when conventional treatment fails or when it is not possible to treat chronically, but also, in some instances, as first choice.

Polyunsaturated fatty acids: Inflammatory bowel disease: Fish oil: Eicosapentaenoic acid: Docosahexaenoic acid

The causes of inflammatory bowel disease (IBD) are as yet unknown. The hypothesis that there is an abnormal immunological response to an altered antigen, either viral or bacterial, is supported by much scientific evidence. All the diseases share an immunological pathogenesis, involving mainly the T- and B-cells, the cytokine network and the complement system, resulting in an inflammatory condition that becomes chronic and self-perpetuating. The amplification of this inflammatory response is controlled by soluble mediators; a long list of mediators with putative roles in IBD has been established (Lauritsen *et al*. 1989). The rationale for *n*-3 long-chain polyunsaturated fatty acids (PUFA) supplementation in the treatment of ulcerative colitis (UC) and Crohn's disease (CD) resides in the anti-inflammatory effects of these lipid compounds. Over the last few years a growing body of evidence has demonstrated that *n*-3 PUFA alleviate a number of inflammatory diseases. In fact, the first evidence of the importance of dietary intake of these lipids was derived from epidemiological observations of a very low incidence of chronic inflammatory conditions in Eskimos (Kromann & Green, 1980).

Dietary eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the two major components of fish oil, partially replace arachidonic acid (the initiating component of the homonymous metabolic pathway) in a time- and dose-dependent manner in plasma and cellular phospholipids. As EPA and DHA are less readily released on cell stimulation, they reduce substrate availability for eicosanoid generation. In addition, the *n*-3 PUFA reduce the production of the 2-series eicosanoids, which are generated by arachidonic acid metabolism and are all pro-inflammatory. These eicosanoids include leukotriene (LT) B_4, which is the most potent chemotactic agent and responsible for neutrophil recruitment (Ford-Hutchinson, 1980), as well as thromboxane A_2, which participates in the inflammatory process by increasing vascular permeability, promoting platelet aggregation and causing oedema (Rampton & Collins, 1993). *n*-3 PUFA also serve as precursors of a class of eicosanoids without inflammatory properties, such as LTB_5 (Lee *et al*. 1985). It has also been widely demonstrated that *n*-3 fatty acids such as EPA and DHA are able to inhibit inflammatory cytokine production (Endres *et al*. 1989). Cytokines belong to a class of soluble proteins that influence the immune cell system, resulting in enhancement of the production of chronic inflammatory substances such as interleukins 1β, 2 and 6 and tumour

Abbreviations: CD, Crohn's disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IBD, inflammatory bowel disease; LT, leukotriene; PUFA, polyunsaturated fatty acids; UC, ulcerative colitis.

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necrosis factor (Endres & von Schacky, 1996; Calder, 1997). *n*-3 PUFA may also be acting as free radical scavengers (Payan *et al*. 1986).

Crohn's disease and ulcerative colitis

n-3 Polyunsaturated fatty acid trials

Studies on the role of *n*-3 PUFA in IBD, UC and CD started at the end of the 1980s. Recent epidemiological evidence concerning the incidence of IBD in Japan has indicated that increasing incidence of CD is strongly correlated with, among other factors, *n*-6: *n*-3 PUFA intake (*r* 0·792); Shoda *et al*. (1996) suggested that increased dietary intake of *n*-6 PUFA with lower levels of *n*-3 PUFA may contribute to the development of CD. Moreover, multifocal gastrointestinal infarctions have been suggested as one of the first pathogenic steps in IBD (Wakefield *et al*. 1989), thus suggesting a pivotal role for platelets and possibly for the powerful platelet aggregator thromboxane A_2 (Lee *et al*. 1985); treatment with *n*-3 PUFA has been shown to decrease platelet responsiveness in patients with IBD (Jaschoenek *et al*. 1991).

It has also been demonstrated that fish oil supplementation improves the nutritional status of rats in which short bowel syndrome, a clinical condition that may also affect patients with CD after multiple surgical bowel resections, was induced. These results were obtained by inducing enterocyte hyperplasia, which markedly increases the mucosal surface area with a corresponding increase in enteral absorption (Vanderhoof *et al*. 1994). Furthermore, it has been shown recently that increasing dietary PUFA intake in patients with IBD may enhance (by 65%) the absorption and the utilisation of saturated fatty acids such as palmitic acid, improving the overall nutritional status (French *et al*. 1997).

From the clinical point of view, the first evidence of clinical benefit was reported by McCall *et al*. (1989) who, in an open study, treated six patients with active UC by giving 3–4 g EPA daily (sixteen to twenty-four capsules of fish oil as triacylglycerol) for 12 weeks and obtained an improvement in symptoms and in histological appearance, as well as a marked fall in LTB_4 neutrophil production. Salomon *et al*. (1990), in another open study, treated ten patients with UC who were refractory to conventional treatment (steroids and salicylates) and obtained an improvement in all the activity variables in seven of ten patients.

The first prospective controlled double-blind study was published by Lorenz *et al*. (1989), who treated thirty-nine patients with IBD, of which twenty-nine had CD in different stages of clinical activity, in a 7-month controlled crossover trial. Patients were randomized to receive either 3·2 g *n*-3 PUFA or olive oil as a placebo/d. Conventional treatment was discontinued whenever possible, otherwise it was minimized and kept constant for at least 3 weeks before the study and until completion. Between the two treatments there was a 1-month wash-out period. At the end of the study the clinical activity, expressed as the CD activity index (Best *et al*. 1976), in patients with CD was unchanged by *n*-3 PUFA supplementation. It is also very important to consider that in this study the crossover design with a very short wash-out period between the two treatments did not allow complete displacement of the additional *n*-3 PUFA from cellular membranes, and could have interfered with the final results of the studies, since it has been demonstrated that the biological effect of the *n*-3 PUFA, i.e. inhibition of cytokine production, persists for >10 weeks after suspension of *n*-3 PUFA (Endres *et al*. 1989).

Hawthorne *et al*. (1992) published the first large placebo-controlled study. In this study ninety-six patients with UC in different stages of activity were enrolled and were given 4·5 g EPA as triacylglycerol/d for 1 year. The patients in the placebo group received olive oil. In patients with active disease at entry it was possible to demonstrate a marked steroid-sparing effect, but fish oil failed to prevent clinical relapse in the group of patients enrolled in remission. Remarkably, the LTB_4 production in stimulated neutrophils was reduced by $>50\%$.

Stenson *et al*. (1992) carried out a randomized double-blind placebo-controlled crossover study in twenty-four patients with active UC treated with 5·4 g *n*-3 PUFA as triacylglycerol (eighteen capsules daily) or olive oil as the placebo/d. The patients received treatment for 4 months followed by 1 month of wash-out. The study demonstrated that fish oil was able to induce a marked gain in body weight, a large improvement in the histology score and a 60% reduction in the LTB_4 production in rectal dialysates. There was no significant steroid-sparing effect compared with the placebo and the improvement in the endoscopy score did not reach a significant level ($P = 0{\cdot}06$).

Aslan & Triadafilopoulos (1992) carried out a similar placebo-controlled crossover trial by giving 4·2 g *n*-3 PUFA or maize oil as the placebo/d. Seventeen patients with active UC received treatment for 3 months followed by a 2-month wash-out period. In 72% of the patients a steroid-sparing effect was seen and in 56% of the patients the activity score of the disease improved markedly. Improvement in the histology score did not reach statistical significance.

Maté *et al*. (1993) reported preliminary data on a group of thirty-eight patients with CD in clinical and laboratory remission, characterized by a CD activity index of <150. The patients were allocated to two groups: group A included nineteen patients who were asked not to change their eating habits and not to use drugs; group B included nineteen patients who received a diet with high levels of fish oil (100–250 g fish daily) for 2 years. At the end of the study six patients in group A and four in group B had left the trial. Among patients who ended the study seven of thirteen in group A had relapsed (54%) and three of fifteen in group B had relapsed (20%). Thus, those receiving the *n*-3 PUFA-enriched diet seem to have prolonged remission.

More recently, Loeschke *et al*. (1996) presented data from a placebo-controlled trial on the prevention of UC relapse. Sixty-four patients in remission were randomized to receive 5 g *n*-3 PUFA as ethyl esters or maize oil as the placebo/d for 2 years. The ongoing treatment with 5-aminosalicylic acid was allowed for 3 months. Very interestingly, after 3 months of the study the fish oil group had fewer relapses than the placebo group ($P < 0{\cdot}02$), but this beneficial effect was lost by the end of the study (2 years). We can speculate that perhaps fish oil and 5-aminosalicylic acid have synergetic effects, and also that

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patient compliance in the fish oil group decreased during the study and could have affected the clinical outcome.

Lorenz-Meyer *et al*. (1996) published data from a large placebo-controlled trial in 204 patients with CD. Patients were included after an acute relapse of their disease in which remission (CD activity index < 150) was obtained under steroid therapy. Patients were randomized to receive *n*-3 PUFA (*n* 70; 5·1 g fish oil as ethyl esters/d), a carbohydrate-reduced diet (*n* 69; 72 g/d) or a placebo (*n* 65; 5 g maize oil/d) for 1 year. Low-dose prednisolone was given to all patients for the first 8 weeks of the trial and then discontinued. On an intent-to-treat analysis none of the treatments were able to prevent clinical flare-up, but the diet poor in carbohydrates, although it was associated with the highest drop-out rate (twenty of sixty-nine; 35%), seemed to be effective ($P < 0{\cdot}05$).

It is very important to mention that the characteristics of the patients with CD in this interesting study represent a big challenge for gastroenterologists. It is well known that patients with CD receiving steroids for an acute flare-up of the disease have > 60% possibility of relapse in the subsequent 6-month period after the suspension of steroid treatment (Brignola *et al*. 1994*a*), and that quite often these patients become steroid-dependent. Due to the strong side effects of steroids in long-term treatment, most of these patients are transferred to an immunosuppressant treatment, which represents the most potent class of drugs available for treating CD.

Some criticism can be made of the choice of placebos. In many of these studies, the placebo was olive oil, which may have interfered with the final end point of these trials (Budiarso, 1990; Petroni *et al*. 1995, 1997; Grimble, 1996). Even the use of maize oil as a placebo is problematic. Maize oil is a rich source of linoleic acid, an essential *n*-6 PUFA which is desaturated and elongated to dihomo-γ-linolenic acid, a precursor of the 1-series of prostanoids which have been claimed to have anti-inflammatory properties in many chronic inflammatory disorders (Payan *et al*. 1986).

The crossover design of most of these studies, with a short wash-out period between the two treatments, may not allow for complete displacement of the additional *n*-3-PUFA from the membrane, and could have interfered with the final results of the studies (Endres *et al*. 1989).

Moreover, in many of the studies in which high doses of fish oil were used, poor patient compliance was registered (Kunzel & Bertsch, 1990; Appel *et al*. 1992; O'Connors *et al*. 1992). This low compliance rate was induced by poor palatability and by minor but very unpleasant side effects such as halitosis, belching and diarrhoea. These effects were related to the high daily intake of fish oil preparations necessary to obtain a satisfactory intestinal absorption and incorporation of *n*-3 PUFA into membranes. Moreover, in two recent studies the intestinal absorption of three different chemical formulations of fish oil (as the triacylglycerol, ester or free fatty acid) was compared and the absorption of the dose administered was found to be 60, 20 and 95% respectively. The better absorption of the free fatty acid formulation may be due to its ability to cross the intestinal wall without requiring the action of lipases, the availability of which could be a limiting factor in the absorption of the other chemical forms (El Boustani *et al*. 1987; Lawson & Hughes, 1988). More recently, it has been shown that even the *in vitro* lipase-mediated clearance of *n*-3 PUFA emulsions from plasma is reduced when compared with that of other long-chain triacylglycerol emulsions, i.e. soyabean oil, and thus reducing free fatty acid availability (Oliveira *et al*. 1997).

For all these reasons, we investigated the ability of a new fish oil derivative to modify the phospholipid-fatty acid profile of plasma and erythrocytes in a group of patients with CD by measuring its fatty acid absorption and incorporation (Belluzzi *et al*. 1994). This new fish oil formulation had two main characteristics, it was a free fatty acid mixture of 45% (w/w) EPA and 20% (w/w) DHA and was coated in three different ways to minimize the fish oil side effects. The pills were coated with a special gastro-resistant coating, to avoid rupture of the capsules in the stomach and to achieve delivery of the *n*-3 PUFA to the first part of the small intestine.

Our data showed that there was apparently much better absorption of the free fatty acid mixture in comparison with the traditional triacylglycerol mixture, and that the double mechanism of release achieved the best absorption and incorporation. We then investigated the possible beneficial effects of this new *n*-3 PUFA preparation in the maintenance of remission in patients with CD (Belluzzi *et al*. 1996).

Our patients were in clinical remission for < 24 months before the study, and all had some laboratory evidence of inflammation. Patients of this type have about 75% greater risk of relapse in comparison with patients who are in remission longer and have normal laboratory tests (Brignola *et al* 1994*b*). Seventy-eight patients were enrolled in the 1-year study. The patients were randomly assigned to receive either three enteric-coated capsules of fish oil three times daily or three enteric-coated capsules of identical appearance containing 500 mg placebo three times daily (the placebo contained a mixed acid triacylglycerol of fractionated fatty acids (%; w/w): 60 capryl acid, 40 capric acid). The fish oil capsules contained 500 mg of a new marine lipid concentrate in free fatty acid form (% (w/w); 40 EPA, 20 DHA) resulting in daily doses of 1·8 g EPA and 0·9 g DHA. The capsules were specially coated to resist gastric acid for at least 30 min and to disintegrate within 60 min. After 1 year, of the thirty-nine patients in the fish oil group, one patient had withdrawn (moved away), four had dropped out because of diarrhoea and eleven had relapsed. Of the thirty-nine patients in the placebo group, one patient had withdrawn (moved away), one dropped out because of diarrhoea and twenty-seven had relapsed (intent-to-treat analysis: relapse rate 41% in fish oil group *v.* 74% in the placebo group, difference 33 (95% CI 13, 54) %, $P = 0{\cdot}003$). In the five patients with diarrhoea, this side effect 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. After 1 year of treatment 59% of the patients in the fish oil group were still in remission, as compared with only 26% in the placebo group ($P = 0{\cdot}006$). Multivariate logistic regression analysis indicated that only fish oil treatment reduced the likelihood of relapse (odds ratio 4·2 (95% CI 1·6, 10·7)).

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