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Double-blind, placebo-controlled study to evaluate the efficacy of fish oil and low-dose UVB in the treatment of psoriasis

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SUMMARY

Since eicosanoids have been implicated in the pathogenesis of psoriasis, less potent eicosanoid mediators derived from fish oil might improve psoriasis. Using a double-blind, randomized, parallel design, 18 patients with stable, plaque psoriasis received capsules of either fish oil or identical-appearing placebo olive oil for 15 weeks, with concomitant sub-erythemal UVB in weeks 3 to 11. At the conclusion of phototherapy, and 4 weeks later, patients in the fish oil group had a greater decrease in the total body surface area of psoriasis and more improvement compared to patients in the olive oil group. The improvement in the fish oil group was statistically significantly greater for all parameters compared to the change in the olive oil group. The apparent safety and general health-promoting features of fish oil could provide an ideal adjunctive therapy for psoriasis.

The oils of cold water fish are rich in long-chain polyunsaturated fatty acids, in particular those of the omega-3 series, e.g., eicosapentaenoic acid (EPA, 20 carbons and 5 double bonds, 20:5) and docosahexaenoic acid (DCHA, 22 carbon atoms and 6 double bonds, 22:6). Omega-3 indicates that the first double bond of the fatty acid, counting from the methyl end, occurs at the third bond. The polyunsaturated acids of fish oil have biological effects that differ from those in vegetable oil, such as linoleic acid, which belong to the omega-6 series.

In involved plaques of psoriasis there is a marked increase in the levels of eicosanoids, e.g. arachidonic acid (AA), leukotriene B_4 and 12-hydroxyeicosatetraenoic acid (12-HETE).[1] In psoriasis, the 5-lipoxygenase pathway which converts AA to leukotrienes is enhanced and is associated with inflammation and cell proliferation. EPA can compete with AA as a substrate for

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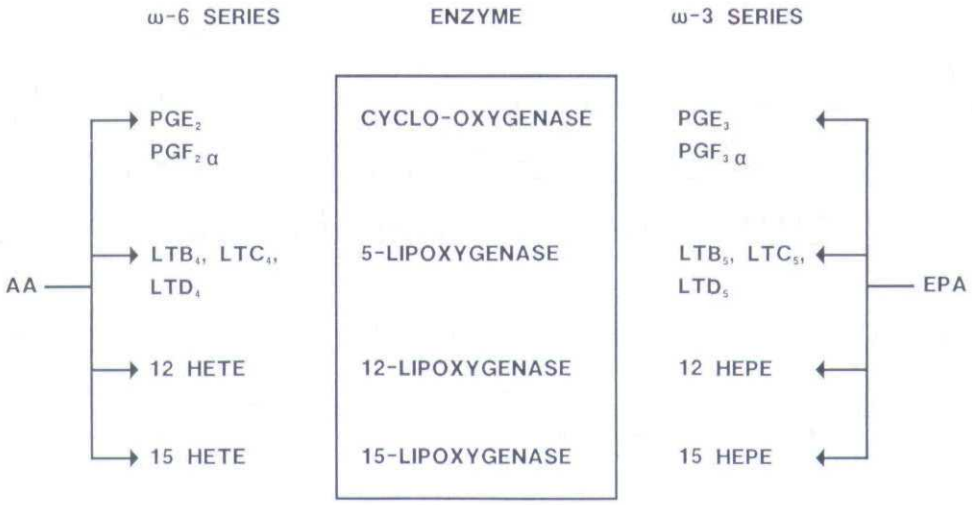

FIGURE 1. Diagram showing the metabolism of arachidonic acid and eicosapentaenoic acid (PG, prostaglandin; LT, leukotriene; HETE, hydroxyeicosatetraenoic acid; EPA, eicosapentaenoic acid; DCHA, docosahexaenoic acid; HEPE, hydroxyeicosapentaenoic acid).

cyclo-oxygenase and lipoxygenase with subsequent production of less biologically active metabolites,[2] such as leukotriene B_5 (Fig. 1). A diet rich in EPA would be expected to lead to an increased production of EPA metabolites of the omega-3 series, and a decrease in the metabolites of AA of the omega-6 series (Fig. 1). A reduction in the inflammatory and proliferative components of psoriasis could occur, if dietary fish oil were taken regularly.

Administration of fish oils, containing large amounts of omega-3 fatty acids, have been reported to be of benefit in the treatment of psoriasis[3-8] and atopic dermatitis.[9] We first demonstrated in an 8 week open trial that dietary fish oil supplementation with Max-EPA^R 60–75 gm per day (10·8–13·5 g of EPA) resulted in modest improvement of psoriasis.[3] At similar doses of fish oil (9–12 g of EPA per day) for up to 3 months, other investigators noted clinical improvement in the majority of patients[4,5] Bittiner *et al.*[6,8] found fish oil (1.8 g EPA per day) to have some beneficial effect in psoriasis, whereas Bjorneboe *et al.*[7] reported no such improvement using the same dose of fish oil.

The limited value of fish oil in all these studies suggests that it is not a monotherapy for psoriasis, but should be used as adjunctive therapy to more potent treatments. We decided to carry out a double-blind, randomized, placebo-controlled trial of parallel design to determine the efficacy of combined therapy with fish oil (3·6 gm EPA daily) and suberythemal doses of ultraviolet B (UVB) phototherapy twice weekly in mild to moderate psoriasis.

METHODS

Twenty adult subjects with stable psoriasis vulgaris (10–50% total body surface area [TBSA] involvement) were chosen for this study. All patients had skin Type II or III and had no oral medications for psoriasis for the previous 4 weeks, and no topical therapy other than emollients for 2 weeks. During the course of the study, patients were permitted to use only the experimental therapy and emollients. Patients were asked to follow their normal diet during the

course of therapy. Patients with acute guttate psoriasis, and pregnant or lactating women were excluded. Informed consent was obtained from each patient and the protocol was approved by the review board of the institution.

The subjects were randomly assigned to two groups. One group received 10 fish oil capsules twice daily (for a daily total of 3·6 g of EPA and 2·4 g of DCHA; Max-EPA^R; R.P.Scherer, Troy, Michigan, U.S.A). The other group was given identical appearing capsules containing olive oil (0 mg EPA and DCHA; 76% oleic acid, 9% palmitic acid, 7% linoleic acid, 2% stearic acid; R.P.Scherer, Troy, Michigan, U.S.A). Nine subjects (six males and three females) with a mean age of 41 years (range 25–65) and mean TBSA involvement with psoriasis of $41 \pm 5\%$ received fish oil capsules. Eleven subjects (eight males and three females), with mean age of 51 years (range 22–74) and TSBA $34 \pm 3\%$ received placebo olive oil capsules. Patients were given fish oil (or placebo) for the first 3 weeks of the study (weeks 0–3). At this point concomitant twice weekly therapy with suberythemal doses of UVB phototherapy for the next 8 weeks was initiated (weeks 3–11). For the last 4 weeks of the study (weeks 11–15), only fish or olive oil was given.

For each patient, prior to UVB phototherapy, the minimal erythema dose (MED) required to produce faint erythema was determined. Ultraviolet B therapy was delivered to all patients, utilizing an Ultralight^R phototherapy cabinet. Light therapy was initiated at 80% of the MED dose. In patients with skin type II, the UVB dosage in Joules was increased by a maximum of 10% just prior to the next phototherapy treatment if the patient had no UVB-induced erythema. In patients with skin type III, the corresponding increase was 20%. No increase in the UVB dosage was carried out if erythema was present when the patient reported for a UVB treatment.

Patients were seen on a weekly basis for the first 3 weeks, and then every 2 weeks for the remainder of the study. Compliance was determined by history and by asking the patients to bring with them the medication containers. The severity of psoriasis was determined by measuring the TBSA and using a grading scale that assessed each of the parameters of scale, erythema and thickness (0 = absent, 1 = trace, 2 = mild, 3 = mild–moderate, 4 = moderate, 5 = moderate–severe, 6 = severe).

Changes in scaling, erythema, thickness, TBSA and overall global response between the fish and olive oil groups were compared using the Students' two sample *t*-test. Differences between the two groups were assessed at pretherapy, the initiation of UVB therapy (week 3), the midpoint of UVB therapy (week 7), the conclusion of UVB therapy (week 11), and the end of the study (week 15; 4 weeks off UVB therapy).

Means are reported with a confidence interval of $\pm$ one standard error. All *P* values are two-sided.

RESULTS

Eighteen of 20 patients completed the 15 week study. One patient dropped out from each of the fish and the olive oil groups because of lack of response. Data is presented only for patients completing the study. None of the patients in either group reported any side-effects.

The scale, erythema, thickness and percentage TBSA during the study are shown in Table 1. The sum of the scale, erythema and thickness scores (0 = no disease present to 18 = severe disease) at pretherapy, weeks 3, 7, 11 and 15 are presented in Fig. 2. In both the fish and olive oil groups, the pretherapy severity of psoriasis was of a comparable nature.

In the group receiving fish oil there were four patients with each of skin types II and III; in the

TABLE 1. Psoriasis severity parameters for fish and olive oil groups

Parameter*		Week 0 Pretherapy	Week 3 Oil alone	Week 7 Oil + UVB	Week 11 Oil + UVB	P†	Week 15 Oil alone	P‡	Per cent change at end of study (Week 15) compared to pretherapy
Erythema	FO	3·5 ± 0·3	3·0 ± 0·3	2·2 ± 0·3	2·2 ± 0·3		2·0 ± 0·3	0·02	−43%
	OO	3·5 ± 0·3	3·2 ± 0·2	2·9 ± 0·3	3·0 ± 0·3	NS	3·5 ± 0·5		0%
Thickness	FO	3·3 ± 0·6	3·2 ± 0·4	2·3 ± 0·4	2·0 ± 0·4		1·7 ± 0·4	0·006	−48%
	OO	3·0 ± 0·2	3·0 ± 0·2	2·4 ± 0·3	2·5 ± 0·3	NS	3·2 ± 0·2		7%
Scale	FO	3·1 ± 0·4	2·7 ± 0·5	1·2 ± 0·7	1·6 ± 0·6		2·0 ± 0·7	0·008	−35%
	OO	3·3 ± 0·2	3·1 ± 0·4	2·7 ± 0·3	2·4 ± 0·3	NS	3·4 ± 0·3		+9%
TBSA%	FO	41 ± 5	35 ± 4	32 ± 4	27 ± 4		22 ± 5	0·0001	−46%
	OO	34 ± 3	36 ± 3	36 ± 3	34 ± 5	0·05	45 ± 2		+32%

* Mean ± SE, based on 6 point scale for erythema, thickness, scale; TBSA = % total body surface area involved with psoriasis.

FO = Fish Oil, n = 8; OO = Olive Oil, n = 10.

† By Student's two-sample *t*-test comparing the mean changes for each group from pretherapy to week 11.

‡ By Student's two-sample *t*-test comparing the mean changes for each group from pretherapy to week 15.

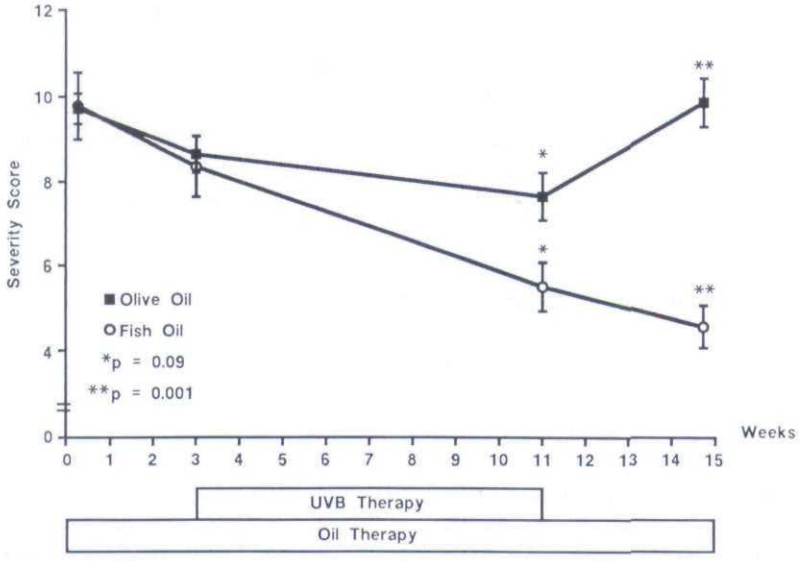

FIGURE 2. Mean sum of scores for scale, erythema, thickness at pretherapy, week 3, week 11 and week 15 in the fish and olive oil groups. Severity score: 0 = no disease and 18 = severe disease; the bars indicate standard error. *P* values were determined by Student's *t*-test comparing the mean sum of scores between the fish and olive oil groups.

olive oil group, there were five patients with each of skin types II and III. Between weeks 3 and 11, the mean total amount of UVB received by the fish and olive oil groups was $1{\cdot}6 \pm 0{\cdot}2$ Joules and $1{\cdot}4 \pm 0{\cdot}3$ Joules, respectively ($P = \text{NS}$).

At the end of week 3, the group receiving fish oil appeared to be improving more than the olive oil group (Table 1). At week 11 the group receiving fish oil had improved to a greater extent compared to pretherapy, than the patients receiving olive oil ($P = 0{\cdot}05$ for TBSA) (Table 1). At week 15, the fish oil group had a 35% decrease in scale compared to pretherapy, while the group receiving olive oil had a 9% increase; the comparable figures for erythema, thickness and TBSA were -43% vs. 0%, -48% vs. $+7\%$ and -46% vs. 32% respectively. For both the fish and olive oil groups, the mean change in the scale, erythema, thickness and TBSA scores between end of therapy (week 15) and pretherapy were calculated and the fish oil group had a statistically significantly better response for all parameters (Table 1, Figure 2).

DISCUSSION

In our experience,[3] fish oil, even at high doses, is not a practical monotherapy for psoriasis. This has also been reported in other studies in which psoriasis demonstrated only mild to moderate improvement[4,5,6,8] or no improvement.[7] In this study, there was no statistical advantage of fish oil over olive oil therapy in the first 3 weeks when oil therapy alone was used. After an additional 8 weeks of oil therapy combined with UVB treatment, we determined that the group receiving fish oil had a decrease in total body surface area, while the group receiving olive oil had no change in this parameter ($P = 0{\cdot}05$) (Table 1). After UV therapy had been stopped and oil therapy alone continued for 4 weeks, the fish oil group improved in all parameters studied compared to pretherapy while the group receiving olive oil had not changed or had worsened. The improvement in the fish oil group was statistically significantly greater for all parameters compared to the change in the olive oil group. These data show that improvement caused by fish oil and low dose UVB at week 11 was maintained for a further 4 weeks by fish oil therapy but not by olive oil administration.

Twice weekly suberythemal UVB for 8 weeks is generally not sufficient as a monotherapy to clear psoriasis. Our UVB protocol was designed to be only minimally effective so as to maximize the relative effect of fish oil. With our study design, it is difficult to accurately determine the contribution of UVB relative to fish oil therapy toward the improvement in psoriasis. However, the degree of improvement noted in the group receiving low dose UVB and fish oil therapy was greater than would be expected following monotherapy with fish oil.

At the doses of fish oil (10·8–13·5 gm of EPA) used in our first study,[3] no adverse side-effects were noted other than occasional 'fishy taste' on the breath upon eructation. In the present study, fish oil and placebo were given in identical-appearing tasteless, gelatinous capsules. In this dose and form, patients noted no 'fishy taste' on the breath upon eructation. Other studies,[4–8] using similar or lower doses of fish oil for the treatment of psoriasis, have not reported side-effects. However, Saynor *et al.*[10] found that patients who took 3·6 g of EPA daily for 2 years had significantly elevated bleeding times compared to those patients receiving 1·8 g of EPA per day. The clinical significance of this is not clear, since in one study the effect on platelets in patients taking 10 g of EPA per day for 1 month was less than occurs with one aspirin tablet (325 mg) taken daily.[11] It may be advisable not to prescribe fish oil to patients with bleeding disorders who are at risk for haemorrhagic complications.

Therapy with fish oil has other advantages besides its value in the treatment of the skin disease.[12] In both normal and hyperlipidaemic subjects, dietary supplementation with fish oil

rich in EPA and DCHA may result in reduction of serum triglycerides, cholesterol, and cholesterol-rich low density lipoproteins (LDL),[13,14] and an elevation of serum high density cholesterol.[15,16] Marsden[17,18] and Lowe *et al.*[19] have shown that supplementation of diet with Max-EPA^R reduces hyperlipidaemia induced by isotretinoin and etretinate. Thus the addition of fish oil to retinoid therapy for psoriasis may lead to a more desirable lipid profile, plus a modestly added therapeutic benefit. Some studies have reported that supplementation of the diet with fish oil may result in a reduction of platelet aggregation, blood viscosity and thrombotic tendency.[20-22] Fish oil in the diet may also exert other cardioprotective effects. Kromhout *et al.*[23] studied fish consumption in 852 middle aged men without coronary heart disease in the Netherlands. They were followed longitudinally for 20 years. Mortality from coronary heart disease was more than 50% lower among those who consumed at least 30 g of fish per day compared to those who did not eat fish. Omega-3 fatty acids have also been reported to reduce blood pressure.[12]

Since fish oil therapy is practical, has certain other potential advantages and a relative lack of side-effects, combination therapy of UVB and fish oil should be considered in the treatment of psoriasis. Fish oil administration may also provide a therapeutic advantage when combined with other therapies for psoriasis. Further studies need to be carried out to determine whether combined therapy with fish oil can lengthen the period of remission in patients with psoriasis.

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