Cod liver oil (*n*-3 fatty acids) as an non-steroidal anti-inflammatory drug sparing agent in rheumatoid arthritis

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Objectives. Dose-dependant gastrointestinal and cardiovascular side-effects limit the use of NSAIDs in the management of RA. The *n*-3 essential fatty acids (EFAs) have previously demonstrated some anti-inflammatory and NSAID-sparing properties. The objective of this study was to determine whether cod liver oil supplementation helps reduce daily NSAID requirement of patients with RA.

Methods. Dual-centre, double-blind placebo-controlled randomized study of 9 months' duration. Ninety-seven patients with RA were randomized to take either 10 g of cod liver oil containing 2.2 g of *n*-3 EFAs or air-filled identical placebo capsules. Documentation of NSAID daily requirement, clinical and laboratory parameters of RA disease activity and safety checks were done at 0, 4, 12, 24 and 36 weeks. At 12 weeks, patients were instructed to gradually reduce, and if possible, stop their NSAID intake. Relative reduction of daily NSAID requirement by >30% after 9 months was the primary outcome measure.

Results. Fifty-eight patients (60%) completed the study. Out of 49 patients 19 (39%) in the cod liver oil group and out of 48 patients 5 (10%) in the placebo group were able to reduce their daily NSAID requirement by >30% ($P = 0.002$, chi-squared test). No differences between the groups were observed in the clinical parameters of RA disease activity or in the side-effects observed.

Conclusions. This study suggests that cod liver oil supplements containing *n*-3 fatty acids can be used as NSAID-sparing agents in RA patients.

KEY WORDS: RA, Fish oil, *n*-3 fatty acids, NSAIDs.

Introduction

RA is a chronic autoimmune inflammatory joint disease in which inflammation plays a key role. Pharmacotherapy with NSAIDs, DMARDs and biologic agents is the cornerstone of treatment, with NSAIDs being frequently used for symptomatic control of pain.

Although NSAID are widely prescribed in RA, concerns about their side-effects have limited their use. Furthermore, with the recent finding that selective cyclo-oxygenase-2 (COX-2) inhibitors are associated with an increased frequency of cardiovascular (CV) events, concerns about the CV safety of the non-selective NSAID have been raised, prompting the search for alternative medications.

The potential anti-inflammatory effects of essential fatty acids (EFAs) were suggested by epidemiological studies in Greenland Eskimos, where *n*-3 fatty acid intake from seafood is high and there is lower prevalence of autoimmune and inflammatory conditions [1]. This concept has now been supported by several studies [2].

Dietary EFAs are precursors of prostaglandins (PGs) and leucotrienes (LTs) both of which are inflammatory mediators. There are different series of PGs and LTs with various pro- or anti-inflammatory properties. As EFA competition for the metabolic enzymes occurs in their production, altering the EFA content in the diet, or by administration of supplements, can modify the type of PGs and LTs formed [3]. Western diets are rich in *n*-6 but low in *n*-3 EFA. The most potent inflammatory PGs (those of the two series) originate from *n*-6 EFA arachidonic acid. The *n*-3 EFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on the other hand, originate from fish oils. EPA competitively inhibits the production of PGs and LTs derived from arachidonic acid and is a precursor of the less inflammatory series-3 PGs and series-5 LTs [2]. Increasing the ingestion of *n*-3 EFAs may result in a reduction of inflammation via these and other mechanisms [4].

Several groups including ourselves have looked at the effect of DHA and EPA in RA. These studies have shown significant improvement in at least two clinical variables of disease activity in patients taking *n*-3 EFA [5]. Additionally, we and others have reported a significant decrease in NSAID requirement in patients taking fish oils [6–8]. Although these studies were double blind and placebo controlled, most have been short, with small numbers of patients, based in one centre only, and did not include a reduction of NSAID requirement as their primary end point.

The objective of this study was to determine whether Seven Seas Marine Oil 1 (SSMO1), an *n*-3 long-chain EFA-rich clinical grade high-strength cod liver oil, helps to reduce the daily NSAID requirement of patients with RA by at least 30% without any worsening of their disease activity.

Patients and methods

Study design

This was a randomized, prospective, investigator-initiated dual-centre, double-blind placebo-controlled study carried out between August 1997 and December 2002. Patients were recruited from the rheumatology departments in Ninewells Hospital and Medical school, Dundee and the Western General Hospital in Edinburgh, UK. Randomization was done separately in each of the two study centres. The randomization code was generated manually in blocks of 10. Patient's consent was obtained according to the Declaration of Helsinki. This study was approved by the Tayside Committee on Medical Ethics and the Lothian Research Ethics Committee.

Patient selection

Ninety-seven patients aged 18 yrs or over and with RA as defined by the ARA [9] were enrolled, and gave written informed consent. The inclusion criteria were, stable RA disease activity and RA

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medication for at least 3 months prior to entering the study, regular NSAID therapy and Steinbrocker functional class I, II or III [10]. The exclusion criteria included ongoing RA disease activity requiring change of therapy, prednisolone at a daily dose >7.5 mg/day, severe intercurrent illness or patients routinely taking supplements containing EPA or other EFA.

Patients were randomly allocated to receive either 10 g of SSMO1 a day (10 capsules) or identical air-filled placebo capsules for 9 months. SSMO1 is a blend of cod liver oil and fish oil and each 1000 mg capsule contains 150 mg of EPA (C20: 5 *n*-3), 70 mg of DHA (C22: 6 *n*-3), 80 µg of vitamin A, 0.5 µg of vitamin D and 2.0 IU of vitamin E.

Clinical assessment

Patients were assessed at baseline, 4, 12, 24 and 36 weeks. The week 4 visit was mainly a safety and compliance assessment. During the other visits, a clinical evaluation was performed that consisted of 28 tender joint count, 28 swollen joint count, grip strength, duration of early morning stiffness (EMS), visual analogue scale (VAS) of pain (100 mm), Stanford HAQ [11] and subjective response (patients were asked whether they were better, the same or worse at each visit).

Bloods were taken for full blood count, biochemistry, CRP and IgM RF.

Patients NSAID dose at baseline was assigned as 100%. NSAID dose reductions were calculated from the baseline. Those patients taking daily preparations once had their NSAID changed to a shorter-acting equivalent of the total dose, e.g. diclofenac slow-release 75 mg twice a day was changed to six 25 mg tablets of diclofenac a day. Patients were asked to document their daily NSAID intake and the average daily requirement from the previous visit was compared with the baseline dose. Any reduction or increase in NSAID dose was documented in percentages. All patients were encouraged to reduce the dosage of their NSAID from the 12-week visit, with the aim of stopping them if possible.

Outcome measures

The primary outcome measure was relative reduction of daily NSAID requirement by >30% after 9 months. Secondary outcome measures were stability or improvements in disease activity score-28 three variables (DAS-28 3v)-CRP, HAQ, VAS pain, grip strength, EMS and subjective response.

Assessment of compliance and safety parameters

Compliance was assessed by counting the total number of returned capsules and by measuring EPA levels in plasma at baseline and after 3 and 9 months. Safety was assessed by routine laboratory tests and patients were asked to report any adverse events encountered.

Power calculation

Power calculation suggested that with a sample size of 47 patients per treatment group, it would be possible to detect a mean difference in the daily NSAID requirement of >30% with a probability of 90% at a predetermined level of $P < 0.05$ (two sided), assuming an S.D. of 45% [12].

Statistical analysis

Analysis was performed by intention to treat. The missing data were completed as follows: for the primary outcome (relative reduction of daily NSAID requirement by >30% after 9 months) a non-completer imputation, in which non-completers were assumed to have had no reduction in NSAID consumption, was done. For the secondary outcomes, the last datum was used in place of any missing follow-up values (last data carried forward).

TABLE 1. Baseline characteristics of study patients

	SSMO1 group	Placebo group
Number of patients	49	48
Age (yrs)	58	61
Female/male (*n*)	34/15	35/13
Disease duration (yrs)	13 ± 1.26	13 ± 1.4
EMS (min)	67 ± 10	74. ± 30
Right grip strength (mmHg)	169 ± 13	170 ± 13
Left grip strength (mmHg)	169 ± 13	166 ± 13
Number of tender joints	8 ± 0.9	9 ± 0.9
Number of swollen joints	8 ± 0.7	7 ± 0.7
CRP (mg/l)	18 ± 3.8	15 ± 2.5
DAS-28-CRP	4.5 ± 0.15	4.5 ± 0.16
VAS pain (mm)	38 ± 2.8	31 ± 2.8
HAQ	1.47 ± 0.10	1.46 ± 0.12
Log_{10} IgM RF	1.79 ± 0.11	1.86 ± 0.09

Values are mean ± S.E.M.

SPSS and Minitab statistical packages were used for all statistical analyses. Two-tailed independent Student's *t*-test was used to compare the distribution of quantitative variables between the treatment groups and chi-squared tests for categorical variables. To estimate differences between treatments, 95% CIs were used.

Results

Ninety-seven patients (52 patients in Dundee and 45 in Edinburgh) aged 37–78 yrs were enrolled in the trial. Of these, 69 were females and 28 males. Both groups were similar in their baseline characteristics (Table 1). All patients were on NSAIDs and 36 (75%) of placebo patients and 39 (79.6%) of the SSMO1 patients were on DMARDs. Only two patients in each group were on more than one DMARD. The two most frequently used DMARDs in both groups were methotrexate and sulphasalazine (taken by 32 and 31% of patients, respectively). Seven (16%) patients in the placebo group and 9 (18%) of those in the SSMO1 group were on oral prednisolone at doses of ≤7.5 mg/day [mean dose 4.9 mg (3–7.5 mg)].

Thirty-two out of 49 (65%) patients in the SSMO1 group and 26 out of 48 (54%) patients in the placebo group completed the study (Fig. 1). Four patients in the SSMO1 group and three in the placebo group had their DMARD or prednisolone dose increased. As these changes in their anti-rheumatic drugs can influence the primary outcome of the study, a secondary analysis was also carried out excluding these patients.

Compliance

Mean (± S.D.) plasma EPA levels (expressed as percentage of total fatty acids) at 3 and 9 months were significantly higher in the SSMO1 (8.67 ± 5% and 8.13 ± 5%, respectively) than in the placebo group (2.96 ± 2% and 3.04 ± 2%, respectively) ($P < 0.0001$, independent sample *t*-test; CI for difference at 3 and 9 months, 3.94, 7.49 and 3.44, 6.74, respectively) confirming compliance. There were no differences in the number of capsules returned by patients in each group 246 (9.1% of the total number of tablets) returned in the SSMO1 group and 297 (11%) in the placebo group, ($P = 0.722$, independent sample *t*-test; CI for difference, −91.2, 63.5).

NSAID requirements

All patients were on NSAID at baseline. The most common NSAIDs were diclofenac, naproxen and ibuprofen taken by 41, 31 and 4% of patients in the SSMO1 group and by 46, 17 and 10% of patients in the placebo group, respectively.

There was a significant difference in the primary outcome variable between the two groups. Nineteen out of 49 (39%) patients in the SSMO1 group and 5 out of 48 (10%) patients in the
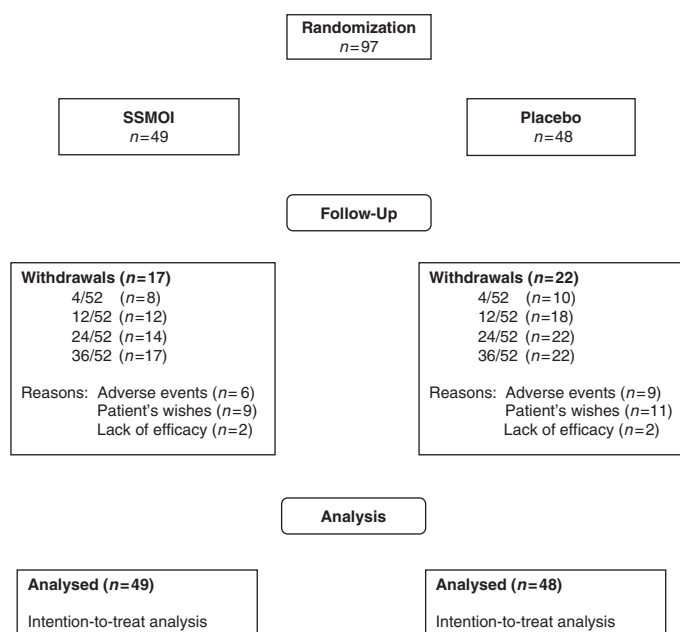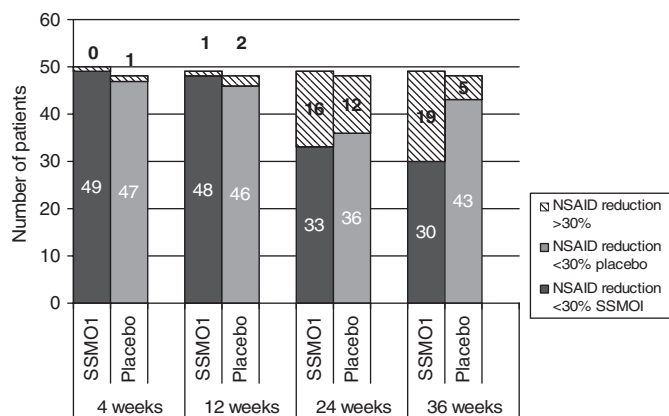
Fig. 1. Participant flow diagram.

Fig. 2. Achievement of 30% reduction in average daily dose of NSAID by treatment.

placebo group were able to reduce their daily NSAID requirement by >30% at 9 months ($P = 0.002$, chi-squared test; 95% CI for difference, 12.2, 44.5) (Fig. 2). Mean ($\pm$ s.e.m.) daily NSAID requirement reduction was also significantly higher in the SSMOI group ($26 \pm 6\%$) than the placebo group ($9 \pm 3\%$) ($P = 0.010$, independent sample t-test; CI for difference, 4.15, 30).

When only those patients who completed the study were analysed; 19 out of 32 (59%) patients in the active group and 5 out of 26 (19%) patients in the placebo group were able to reduce their daily NSAID requirement by >30% at 9 months ($P = 0.003$, chi-squared test; 95% CI for difference, 17.4, 62.9). The mean ($\pm$ s.e.m.) daily NSAID requirement of those patients who completed the study decreased by $40 \pm 7.6\%$ in the SSMO1 group and by $16 \pm 5.5\%$ in the placebo group ($P = 0.021$, independent sample t-test; CI for difference, 3.69, 43.07).

When those patients who had their DMARD or corticosteroid dose increased during the study period were excluded from the analysis, the results remained highly significant with 17 out of 28 (61%) patients in the SSMO1 group and 5 out of 24 (21%) patients in the placebo group being able to reduce their NSAID

daily dose by more than a third ($P = 0.005$, chi-squared test, 95% CI for difference, 15.6, 64.2).

Clinical parameters

The main objective of the study was to assess whether RA patients were able to reduce their NSAID intake without any worsening of their disease activity. This was achieved in all of the clinical parameters studied. There were no statistically significant differences between groups in the HAQ, EMS, DAS-28-CRP, CRP, right and left grip strength (Table 2).

Indeed there was a modest but statistically significant improvement in the mean ($\pm$ s.e.m.) VAS for pain from baseline to the 9-month visit in the SSMO1 group (-6.7 ± 3.05 mm) when compared with the placebo group (1.9 ± 2.40 mm) ($P = 0.029$, independent sample t-test; CI for difference, -16.38, -0.92).

Adverse events and withdrawals

There were no statistically significant differences in the number or type of side-effects reported by patients in the active and placebo groups ($P = 0.709$). Most of the side-effects were mild and consisted of nausea (10 patients in the SSMO1 group and 6 in the placebo group), vomiting (four and two), diarrhoea (nine and five), flatulence or inability to swallow the capsules (seven and six). Six of the patients in the SSMO1 group experienced adverse events considered to be moderate or severe but these were not felt to be related to the study medication (two had cellulitis, one a transient ischaemic attack and three sustained fractures after falling). In the placebo group, 10 patients had moderate-to-severe adverse events but none of these were believed to be related to the study medication (eight mild infections, one myocardial infarction and one deep vein thrombosis).

Seventeen patients (35%) in the SSMO1 group and 22 (46%) in the placebo group withdrew before the end of the study. The main reasons for withdrawal were: (i) adverse events judged to be unrelated to study medication (three in the SSMO1 group and two in the placebo group); (ii) adverse events judged to be related to study medication (three and seven); (iii) voluntary withdrawal (9 and 11); and (iv) lack of efficacy of study medication (two and two). There were no statistically significant differences in the number of withdrawals from the active and placebo groups, or in the type of adverse events that were the cause of withdrawal ($P = 0.304$, chi-squared test; 95% CI for difference, -30.54, 8.26).

Three of the withdrawals from the SSMO1 group were judged to be unrelated to the study medication. One patient developed diverticulitis, one had chest pain believed to be cardiac in origin and the third developed fibrosing alveolitis. In the two patients from the placebo group that withdrew with an adverse event unrelated to the study medication, one had cellulitis and the other developed probable NSAID-induced hypertension. The study medication related adverse events that led to withdrawals were all due to gastrointestinal complaints such as diarrhoea, nausea, vomiting and abdominal bloating.

Voluntary withdrawal unrelated to adverse events was more frequent, with 9 patients in the SSMO1 group and 11 in the placebo group doing so. Among concerns raised by this group of patients were the large size and number of capsules to be taken daily, awareness that the capsules were empty and dislike of the fishy taste of the capsules. The rest of the withdrawals were due to failure to attend study visits or patient's perceived lack of efficacy of the study drugs.

Discussion

To our knowledge this is the largest and the only dual-centre study to have investigated the effect of n-3 EFAs in RA. In this trial, we have shown that a daily intake of 10 g of cod liver oil significantly reduces the daily NSAID requirement by more than a third in 39% of patients with RA that started it and almost two-thirds of

TABLE 2. Clinical and laboratory parameters of study patients

	Baseline			12 weeks			24 weeks			36 weeks		
	SSMOI	Placebo	P-value	SSMOI	Placebo	P-value	SSMOI	Placebo	P-value	SSMOI	Placebo	P-value
DAS-28-CRP	4.5 ± 0.15	4.5 ± 0.16	0.940	4.3 ± 0.16	4.3 ± 0.17	0.976	4.32 ± 0.17	4.35 ± 0.19	0.904	4.42 ± 0.16	4.32 ± 0.20	0.695
CRP (mg/l)	18 ± 3.8	15 ± 2.5	0.491	19 ± 3.8	16 ± 2.2	0.622	18 ± 3.4	19 ± 3.8	0.830	21 ± 3.7	20 ± 3.9	0.908
HAQ	1.47 ± 0.10	1.46 ± 0.12	0.931	1.35 ± 0.11	1.48 ± 0.12	0.454	1.39 ± 0.11	1.45 ± 0.12	0.708	1.39 ± 0.12	1.48 ± 0.12	0.599
VAS pain (mm)	38 ± 2.8	31 ± 2.8	0.094	31 ± 3.1	30 ± 2.6	0.831	29 ± 3.1	32 ± 3.1	0.529	31 ± 3.2	32 ± 3.0	0.820
VAS pain diff. (mm)				-7 ± 2.9	-1 ± 2	0.106	-8.1 ± 3.0	1 ± 2.4	0.013	-6.7 ± 3.05	1.9 ± 2.40	0.029
EMS (min)	67 ± 10	74 ± 30	0.829	48 ± 7	76 ± 30	0.365	49 ± 8	80 ± 30	0.319	44 ± 7	43 ± 6	0.883
Subjective response (B/S/W)				12/22/7	10/24/7	0.908	10/25/6	7/18/16	0.045	17/17/7	10/18/13	0.162
R grip (mmHg)	168 ± 12	170 ± 13	0.900	176 ± 12	161 ± 13	0.425	178 ± 12	159 ± 13	0.298	180 ± 12	165 ± 13	0.397
L grip (mmHg)	169 ± 13	166 ± 13	0.881	172 ± 13	157 ± 12	0.405	169 ± 13	159 ± 12	0.578	191 ± 23	161 ± 12	0.254

Values are mean ± s.e.m. SSMOI ($n=49$) and Placebo ($n=48$). VAS pain diff.: reduction of VAS pain from baseline; Subjective response (B/S/W): number of patients that felt better (B), the same (S) or worse (W) at each visit; R grip: right grip strength; L grip: left grip strength.

patients who continue to take it. This reduction of anti-inflammatory intake was achieved without worsening of disease activity. Indeed, there was a significant improvement in the pain VAS of those patients taking daily SSMO1.

These findings are important at a time when there are increasing concerns about adverse events associated with NSAID use. NSAIDs are among the most frequently prescribed medications worldwide with over 111 million prescriptions being written between September 1999 and August 2000 in the United States [13]. NSAIDs are frequently used in RA with one study reporting regular NSAID use in over 70% of the RA patients studied [14].

NSAID have been linked with important adverse events such as gastrointestinal toxicity, increases in blood pressure, aggravation of heart failure in elderly patients [15] and excess risk of cardiovascular events [16, 17]. This may be particularly important in RA that is known to be associated with increased CV mortality [15].

The potential for side-effects associated with these drugs are prompting patients with RA to seek alternative therapies to manage their disease. Recently, 60–90% of patients with arthritis have been reported to use complementary and alternative medicine options [18].

Few placebo-controlled randomized trials assessing the effect of fish oils on RA disease activity have been published. Of those that have, the majority have shown an improvement in at least two clinical variables or a reduction in the NSAID requirement. These have been summarized by other authors [4, 5, 19]. As most of the studies included only small numbers of patients and were of short duration (≤ 6 months) we were encouraged to undertake a larger two-centre study.

Previous studies, including one from our group, used the reduction of the daily requirement of NSAID as an outcome measure [6–8, 20]; but only in our own previous study [7] and the present trial has NSAID requirement been the main outcome measure, with a specified protocol for the reduction of the NSAID dose. The current study differed from our earlier trial in which patients on DMARD were excluded because of the possibility that these drugs might attenuate the effects of fish oils by interfering with the metabolism of PGs and LTs [21]. As DMARDS are now so widely used in the treatment of patients with RA, exclusion of patients with RA receiving DMARD from the current study would have severely restricted the applicability and clinical relevance of any trial conclusions.

This is the first study in which the proportion of patients achieving a clinically significant NSAID reduction of 30% has been used as the primary outcome measure, rather than simply seeking a statistically significant mean reduction in consumption of NSAID. The results are encouraging with almost two-thirds of patients who continued to take the SSMO1 supplements achieving this goal. A total of 30% was considered an appropriate cut-off point as the risk of upper gastrointestinal bleeding and perforation with NSAID is dose dependent; with those on low/medium daily doses having a 2- to 3-fold increase in relative risk while those patients on high doses may have a >5-fold increase in risk [22].

A limitation of this study was the relatively large number of withdrawals. Most of these were attributable to patient's wishes (particularly patient's unwillingness to take 10 large capsules a day in addition to their regular medication) or gastrointestinal intolerance. Despite the large number of withdrawals observed in this study, 39% of all patients starting SSMO1 were still able to reduce their NSAID daily intake by a third.

We may have compromised the double blinding of the study by using air-filled capsules as placebo. Although it was recognized that some patients would discover their capsules to be empty and others may realize about the capsules lack of 'fishy' smell and taste, air-filled capsules were selected as being the most appropriate placebo available after critical appraisal of alternatives. The possibility of using capsules filled with other fatty acids was rejected as none are believed to be truly inert, and saturated fats may be associated with a health risk.

In summary, we have demonstrated that oral supplements of 2.2 g a day of EPA and DHA reduces the daily intake of NSAIDs by more than a third in almost 40% of patients with RA, without any worsening of their disease activity. Fish oil supplementation should be considered in RA patients to help them reduce their NSAID intake in order to attenuate the risks of gastrointestinal and cardiovascular adverse events associated with these drugs.

Rheumatology key message

- Cod liver oil supplements containing *n*-3 fatty acids can be used as NSAID sparing agents in RA patients.

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