Subjective Improvement in Patients with Psoriatic Arthritis After Short-Term Oral Treatment with Seal Oil. A Pilot Study with Double Blind Comparison to Soy Oil

TOR MAGNE MADLAND, TORMOD BJØRKKJÆR, LINN ANNE BRUNBORG, LIVAR FRØYLAND, ARNOLD BERSTAD, and JOHAN G. BRUN

ABSTRACT. Objective. To investigate effects of short-term oral treatment with seal oil in patients with psoriatic arthritis (PsA).

Methods. Forty-three patients with polyarticular PsA were randomized to receive oral treatment for 2 weeks with either seal oil or soy oil in a double blind controlled trial. Clinical and biochemical variables were assessed at baseline, after treatment, and 4 weeks post-treatment. Patients were allowed to continue nonsteroidal antiinflammatory drugs (NSAID) and disease modifying antirheumatic drugs (DMARD) during the study.

Results. Forty patients completed the study, 20 in each treatment group. Patients in the seal oil group reported a significant improvement in global assessment of the disease 4 weeks post-treatment (p < 0.01), and both groups showed a trend toward improvement in tender joint count, but the differences between the groups were not significant. There was a fall in the ratio of n-6 to n-3 fatty acids and in arachidonic acid (AA) to eicosapentaenoic acid (EPA) in serum after treatment with seal oil (p < 0.01). Twenty-one percent of all patients had elevated values of calprotectin in feces suggestive of asymptomatic colitis.

Conclusion. Treatment with seal oil was followed by a modest improvement in patient’s global assessment of the disease and a trend towards a decrease in number of tender joints. There was a shift in fatty acid composition in serum toward a putative antiinflammatory profile. Oral treatment with seal oil may have NSAID-like effects in PsA. (J Rheumatol 2006;33:307–10)

Key Indexing Terms:
PSORIATIC ARTHRITIS
POLYUNSATURATED FATTY ACIDS
SEAL OIL
SOY OIL
EICOSANOIDS
CALPROTECTIN

Psoriatic arthritis (PsA) belongs to the spondyloarthropathies (SpA), a group of inflammatory diseases with common clinical and genetic characteristics. A significant proportion of patients with SpA have evidence of gut inflammation, and this has been suggested to play a pathogenetic role. Calprotectin has been recognized as a proinflammatory protein in arthritis and related conditions, and increased calprotectin levels in feces may serve as an indicator of intestinal inflammation.

There is substantial evidence that dietary intake of fish oil may have benefits in rheumatoid arthritis (RA), with regard to both inflammation and collateral health. Short-term duodenal administration of seal oil to patients with inflammatory bowel disease (IBD) and related joint pain showed beneficial effects on joint pain in 2 recent studies. Fish oil has high amounts of the n-3 polyunsaturated fatty acids (PUFA) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These have shown modulatory effects on inflammation, mainly antiinflammatory. On the other hand, the n-6 PUFA arachidonic acid (AA) is a precursor of eicosanoids like prostaglandins, leukotrienes, and related compounds with proinflammatory effects. The high ratio of n-6 to n-3 fatty acids (FA) of the Western diet leads to a high ratio of AA to EPA in blood and tissues, which could promote arthritis by facilitating the production of proinflammatory eicosanoids. Of the n-3 PUFA, only EPA, eicosapentaenoic acid (DPA), and DHA are marine, i.e., naturally found in seafood and seafood products. Intake of marine n-3 supplements may result in a decreased production of AA-derived eicosanoids through several mechanisms, including decreased availability of AA, competition for cyclooxygenase (COX) and lipoxygenase (LOX), and decreased expression of COX-2 and 5-LOX. Fish oil and seal oil have approximately the same total amount of n-3 PUFA, but seal oil has more DPA than fish oil. Although there is slightly less EPA and DHA in seal oil than in fish oil,
intake of seal oil increases the serum level of EPA considerably more than intake of fish oil. The n-3 PUFA thus seem to be more available from seal oil than from fish oil, possibly by being located mainly in the middle position of the triacylglycerol (TAG) molecule in fish oil, while located almost exclusively in the 1 or 3 positions in seal oil TAG. Both pancreatic and lipoprotein lipases are position 1 and 3 specific. In daily rheumatology practice we have noticed that some patients use seal oil as a dietary supplement. Based on the above observations, we investigated whether short-term oral treatment with seal oil might have positive effects on disease manifestations in patients with PsA.

MATERIALS AND METHODS

Patients with polyarticular PsA as diagnosed by a rheumatologist and seen with active joint disease at our clinic during the last year were sent a written inquiry to join the study. Polyarticular PsA was defined as polyarthritis (5 or more swollen joints) in a patient with psoriasis, with seronegativity for rheumatoid factor and absence of rheumatoid nodules. The sample number (n = 40) was chosen to provide sufficient power to detect a difference of 10 mm on a 100 mm visual analog scale (VAS) for joint pain or patient’s global assessment before and after treatment. Patients were allowed to continue their usual medication including nonsteroidal anti-inflammatory drugs (NSAID) and disease modifying antirheumatic drugs (DMARD) during the study period. No patients changed their DMARD or received intraarticular glucocorticoids within 4 weeks prior to study start. The Regional Committee for Medical Research Ethics approved the study, and all patients provided written informed consent before inclusion.

Study design. Patients were assessed at the baseline visit, and if eligible for the study, included and randomly allocated to treatment with either seal oil (n = 22) or soy oil (n = 21). Ten milliliters of study oil was self-administered orally before meals 3 times a day for 14 days. The patients were reassessed at week 2 and week 6. All clinical assessments were made by the same physician. The seal oil (Rieber Skinn A/S, Bergen, Norway) was refined oil from harp seal (Phagophilus groenlandicus). Subjects in the seal oil group thus received 2.4 g of EPA, 1.1 g of DPA, and 2.6 g of DHA per day. Soy oil (Mills DA, Oslo, Norway) was selected as control treatment based on its similarity to seal oil in consistency and appearance. The received doses of soy oil correspond to 14.9 g of linoleic acid (LA) per day.

The FA profiles of seal oil and soy oil are presented in Table 1. The treatment groups were comparable regarding gender, age, disease duration, self-reported dietary intake of fish or fish oil, and mean ratio of n-6 to n-3 PUFA in serum. There were no significant differences in disease assessment variables between the groups at baseline, nor in concomitant medication with NSAID. More patients in the soy oil group were receiving some DMARD, but the difference between the groups was not significant (p = 0.05). The mean concentration of calprotectin in feces was equal: 21% of all patients had values above the upper reference value (50 mg/kg). The acute phase reactants (ESR, CRP, and calprotectin in plasma) were correlated at baseline (r = 0.1). The mean ratio of n-6 to n-3 PUFA in serum was 7.2 (2.4) in the seal oil group and 5.8 (3.1) in the soy oil group. The treatment groups were similar regarding disease duration, age, global assessment, and joint pain.

RESULTS

Forty-three patients were included between October 2003 and January 2004. Three subjects did not complete the trial: one because of a sports injury (seal oil), one because of intolerance to the study oil (seal oil), and one gave no reason for dropping out (soy oil). Baseline characteristics of the patients are presented in Table 2. The treatment groups were comparable regarding gender, age, disease duration, self-reported dietary intake of fish or fish oil, and mean ratio of n-6 to n-3 PUFA in serum. There were no significant differences in disease assessment variables between the groups at baseline, nor in concomitant medication with NSAID. More patients in the soy oil group were receiving some DMARD, but the difference between the groups was not significant (p = 0.05). The mean concentration of calprotectin in feces was equal: 21% of all patients had values above the upper reference value (50 mg/kg). The acute phase reactants (ESR, CRP, and calprotectin in plasma) were correlated at baseline (p < 0.05), but calprotectin was the reactant with the highest concentration.
After finishing the study, 25 patients (62.5%) correctly identified which oil they had received according to taste, smell, or consistency.

**DISCUSSION**

Our finding of a significant but modest improvement in patient’s global assessment after oral treatment with seal oil is in agreement with studies of treatment effects of fish oil in RA and seal oil in patients with IBD-related joint pain. Patients treated with seal oil in our study reported an improvement in global assessment of disease but less reduction of joint pain. The treatment may have relieved symptoms that we did not record, like stiffness and fatigue, or the treatment period may have been too short to achieve significant reduction of joint pain. The rapid effect in the 2 latter studies may be related to duodenal rather than oral administration of the seal oil. Duodenal administration might ensure a more rapid absorption by yielding a higher bolus of n-3 PUFA into circulation when administering the oil to the major site of TAG hydrolysis, thus avoiding mixing and dilution in the stomach. Despite lower increase in serum values of n-3 PUFA than Bjorkkjaer, et al reported, we clearly showed absorption of FA from seal oil into the circulation. A shift in FA composition in serum may occur more rapidly after seal oil than fish oil treatment because of the

Table 3. Results of assessment variables for the treatment groups. Results are expressed as median (range). No significant differences between the groups were detectable before and after treatment (Mann Whitney test).

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Seal Oil Week 2</th>
<th>Week 6</th>
<th>Baseline</th>
<th>Soy Oil Week 2</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s global assessment, mm</td>
<td>47 (10–97)</td>
<td>33.5 (4–97)</td>
<td>33 (2–85)*</td>
<td>41.5 (2–81)</td>
<td>33 (1–80)</td>
<td>36.5 (2–71)</td>
</tr>
<tr>
<td>Joint pain intensity, mm</td>
<td>35.5 (13–72)</td>
<td>45.5 (3–84)</td>
<td>31 (5–78)</td>
<td>35 (11–69)</td>
<td>37.5 (1–76)</td>
<td>36.5 (2–66)</td>
</tr>
<tr>
<td>MHAQ (1–4)</td>
<td>1.7 (1–2.5)</td>
<td>1.7 (1–2.6)</td>
<td>1.6 (1–2.8)</td>
<td>1.5 (1–2.3)</td>
<td>1.4 (1–2.3)</td>
<td>1.4 (1–2.2)</td>
</tr>
<tr>
<td>Tender joint count (0–52)</td>
<td>9 (0–37)</td>
<td>7.5 (0–37)</td>
<td>5 (0–29)</td>
<td>10.5 (2–29)</td>
<td>8 (0–29)</td>
<td>7 (0–26)</td>
</tr>
<tr>
<td>Swollen joint count (0–52)</td>
<td>2 (0–11)</td>
<td>2.5 (0–8)</td>
<td>1.5 (0–6)</td>
<td>2 (0–10)</td>
<td>2 (0–13)</td>
<td>2 (0–12)</td>
</tr>
<tr>
<td>Calprotectin, mg/l (100–900)</td>
<td>740 (460–3460)</td>
<td>880 (500–4780)</td>
<td>1000 (360–6640)</td>
<td>1000 (360–5360)</td>
<td>820 (400–4360)</td>
<td>880 (320–7080)</td>
</tr>
</tbody>
</table>

* p < 0.01, changes from baseline within group (Wilcoxon sign rank test).

Table 4. Mean (SD) serum values of cholesterol, homocysteine and fatty acids (expressed as mg/g) for the treatment groups.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Seal Oil Week 2</th>
<th>Week 6</th>
<th>Baseline</th>
<th>Soy Oil Week 2</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>5.5 (1.2)</td>
<td>5.4 (1.1)</td>
<td>5.5 (1.0)</td>
<td>5.8 (0.8)</td>
<td>5.4 (0.8)*</td>
<td>5.9 (0.9)</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/l</td>
<td>1.5 (0.6)</td>
<td>1.6 (0.7)</td>
<td>1.5 (0.5)</td>
<td>1.6 (0.4)</td>
<td>1.6 (0.4)</td>
<td>1.6 (0.4)</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/l</td>
<td>3.5 (1.0)</td>
<td>3.4 (0.8)</td>
<td>3.3 (0.9)</td>
<td>3.8 (0.7)</td>
<td>3.5 (0.7)*</td>
<td>3.9 (0.9)</td>
</tr>
<tr>
<td>Homocysteine, µmol/l</td>
<td>12.0 (3.1)</td>
<td>12.7 (3.0)</td>
<td>12.4 (3.2)</td>
<td>10.3 (4.1)</td>
<td>10.0 (2.7)</td>
<td>9.8 (2.9)</td>
</tr>
<tr>
<td>Linoleic acid**</td>
<td>1.83 (0.48)</td>
<td>1.60 (0.53)</td>
<td>1.72 (0.52)</td>
<td>1.41 (0.33)</td>
<td>1.79 (0.40)*</td>
<td>1.66 (0.51)</td>
</tr>
<tr>
<td>α-linolenic acid**</td>
<td>0.04 (0.17)</td>
<td>0.05 (0.05)</td>
<td>0.05 (0.03)</td>
<td>0.03 (0.02)</td>
<td>0.04 (0.01)*</td>
<td>0.04 (0.03)</td>
</tr>
<tr>
<td>Arachidonic acid</td>
<td>0.32 (0.12)</td>
<td>0.27 (0.11)</td>
<td>0.27 (0.11)</td>
<td>0.25 (0.06)</td>
<td>0.26 (0.05)</td>
<td>0.27 (0.05)</td>
</tr>
<tr>
<td>Eicosapentaenoic acid**</td>
<td>0.09 (0.08)</td>
<td>0.35 (0.19)*</td>
<td>0.15 (0.08)</td>
<td>0.08 (0.06)</td>
<td>0.08 (0.04)</td>
<td>0.09 (0.06)</td>
</tr>
<tr>
<td>Docosapentaenoic acid</td>
<td>0.03 (0.02)</td>
<td>0.05 (0.03)</td>
<td>0.04 (0.02)</td>
<td>0.03 (0.02)</td>
<td>0.03 (0.02)</td>
<td>0.03 (0.01)</td>
</tr>
<tr>
<td>Docosahexaenoic acid</td>
<td>0.19 (0.09)</td>
<td>0.26 (0.11)</td>
<td>0.21 (0.08)</td>
<td>0.15 (0.06)</td>
<td>0.15 (0.05)</td>
<td>0.16 (0.05)</td>
</tr>
<tr>
<td>n-6/n-3 fatty acids**</td>
<td>7.2 (2.4)</td>
<td>3.1 (1.3)*</td>
<td>5.4 (1.4)</td>
<td>6.9 (3.1)</td>
<td>7.5 (2.5)</td>
<td>7.2 (3.6)</td>
</tr>
<tr>
<td>AA/EPA</td>
<td>4.7 (2.2)</td>
<td>1.0 (0.7)*</td>
<td>2.8 (1.6)</td>
<td>5.4 (5.1)</td>
<td>4.3 (2.3)</td>
<td>5.5 (4.7)</td>
</tr>
</tbody>
</table>

* P < 0.01, changes from baseline within group (paired samples t test). ** Significant differences between the groups from week 0 to week 2 (t test, p < 0.01).
the conformity between positioning of the n-3 PUFA in the TAG molecules in seal oil and the specificity of the human lipases. Readily available free n-3 PUFA from seal oil may compete with AA and inhibit its metabolism to eicosanoid production. The PUFA are distributed to and incorporated into cellular membranes throughout the body, and may thereafter be released to generate eicosanoid mediators. This may be one mechanism explaining the beneficial effects of the treatment for several weeks post-treatment, as in our study, and months as recorded by Bjorkkjaer, et al.6. Mechanisms for antiinflammatory effects of n-3 PUFA have been described7,9.

Based on earlier studies of treatment effects of fish or seal oil and the short duration of our study, we looked primarily for symptomatic, NSAID-like effects. Hence, the use of major response criteria for clinical trials such as the psoriatic arthritis response criteria (PsARC), American College of Rheumatology (ACR) criteria, or disease activity scores (DAS) did not seem appropriate. Instead, we assessed several clinically relevant variables, looking for short-term responses to the intervention, with special emphasis on detecting differences in subjective measures.

Patients were allowed to continue NSAID during the study period, and since both n-3 PUFA and NSAID have effects on eicosanoid production through the COX pathway, there is a possibility of interaction. Treatment with FA would have to show effects in addition to those of the NSAID used. Therefore a treatment effect may have been masked.

The fact that only slightly more than 50% of the patients were able to identify which treatment they had received indicates that there was no significant blinding bias. It may be questioned whether soy oil constitutes a valid comparison to seal oil. Since soy oil contains n-6 PUFA, which may affect eicosanoid production, soy oil should not be regarded as a true placebo treatment.

Patients included in the study were homogenous in terms of clinical presentation of PsA with polyarthritides. This was decided in order to overcome the complex outcome measure of axial disease and oligoarthritis, which are other clinical presentations of PsA. The study patients generally had low disease activity as measured with PASI score, number of swollen joints, ESR, and CRP. This may have limited the potential for recording improvement by any treatment. Most patients had normal CRP values, and we therefore also measured inflammatory activity by use of calprotectin. This protein has been shown to be a good indicator of disease activity in various inflammatory rheumatic diseases, especially in RA15. In PsA calprotectin has been found in elevated concentrations both in the synovial membrane and in serum, the latter with significant correlations with systemic variables of disease activity16. We also found high correlations between the inflammatory markers ESR, CRP, and calprotectin in the serum of the study patients. Our finding of high levels of calprotectin in feaces of patients with PsA without symptoms suggesting IBD is in accordance with previous reports17, and indicates that some patients with PsA may have asymptomatic colitis.

In conclusion, we showed a shift in FA composition in serum after treatment with seal oil compared to soy oil towards a putative antiinflammatory profile. Patients treated with seal oil reported a subjective improvement of disease as opposed to patients treated with soy oil, but the difference between the groups was not significant. The results warrant further studies of longer duration and more participants to characterize the magnitude and quality of the treatment effects.

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