



# The Journal of Rheumatology

## EDITORIAL

### **Fish Oil and Rheumatoid Arthritis: Antiinflammatory and Collateral Health Benefits**



In this issue Volker and co-workers add to evidence on the efficacy and tolerability of treatment with fish oil in rheumatoid arthritis (RA). For the first time in a study of RA, the investigators considered avoidance of unnecessary amounts of competitor omega-6 fats in the diet as a way of increasing utilization of omega-3 fats in fish oil supplements<sup>1</sup>. There are now 13 published randomized controlled trials (RCT) of fish oil in late RA (mean disease duration typically > 10 yrs); all indicate modest but consistent benefit against a background of usual pharmacotherapy<sup>2</sup>. All but the more recent studies have been included in megaanalysis (analysis using original data sets) and metaanalysis with confirmation of efficacy of fish oil<sup>3</sup>. Thus, the clinical data achieve the highest standard of proof of efficacy proposed for evidence based medicine (i.e., metaanalysis of RCT). The clinical findings are complemented by data from epidemiological, biochemical, and animal studies for antiinflammatory effects of fish and fish oil<sup>2</sup>. One can conclude that the findings of adjunctive benefit from dietary fish oil in RA treatment are robust, albeit modest, in the setting of late disease in which all studies have been undertaken.

An issue that has received insufficient attention is the potential of dietary omega-3 fats, of which fish oil is a rich source, to deliver collateral health benefits within the context of a Western diet, particularly with regard to cardiovascular risk. This is especially important in RA, where there is evidence of a standardized mortality ratio  $\geq 2$ , which is mostly attributable to increased cardiovascular events<sup>4,5</sup>. Cardiovascular risk in RA may be compounded by pharmacotherapy. For example, methotrexate, especially in combination with sulfasalazine, increases plasma homocysteine, a risk factor for myocardial infarction<sup>6</sup>. Also, methotrexate use was a predictor of mortality in RA patients with cardiovascular comorbidity<sup>7</sup>. Cyclosporin A has hypertensive as well as nephrotoxic effects. Also, a question remains over the potential of cyclooxygenase-2 (COX-2) inhibitors to increase the frequency of thrombotic vascular events through selective inhibition of prostacyclin production (prostacyclin promotes vascular patency and its synthesis is COX-2 mediated) without inhibition of platelet thromboxane production (thromboxane is a vasoconstrictor and proaggregant and its synthesis is COX-1 mediated)<sup>8</sup>.

Dietary intervention studies of secondary prevention of myocardial infarction have shown that increased intake of omega-3 fats from fish and fish oil improves outcomes<sup>9,10</sup>. Risk reduction for sudden death was around 40%<sup>10</sup>. Also, epidemiological studies show low incidence of cardiovascular death in populations that habitually consume liberal amounts of omega-3 fats<sup>11,12</sup>.

Regarding potential mechanisms, eicosapentaenoic acid (EPA) found in fish oil is a competitive inhibitor of arachidonic acid metabolism by COX and results in synthesis of a less thrombogenic mix of eicosanoids<sup>12</sup>. Also, the protective effect of omega-3 fats against sudden cardiac death is mirrored in reduction of experimentally induced arrhythmias in animals and has been attributed to a myocardial membrane effect of omega-3 fats<sup>13,14</sup>.

Thus, dietary fish oil supplements in RA have treatment efficacy and can deliver collateral benefits in terms of reduced cardiovascular risk. No important toxicities have been associated with their use. Notwithstanding, they

are not a component of standard therapy for RA, and although no formal data exist, only a small minority of rheumatologists seem to include fish oil among their recommendations for RA patients. Why are fish oil supplements not used more widely in RA? The answer is manifold. First, fish oil is not a patentable product and therefore there is little commercial incentive to promote its use. Second, the benefits of dietary fish oil supplements are delayed up to 3 to 4 months depending on dose. To implement treatment that has such a delayed effect requires belief in efficacy on the part of the prescriber that must be articulated and transferred to the patient. Regrettably, in the absence of industry driven marketing, few physicians are sufficiently knowledgeable or committed to provide convincing advice. Third, there is a perception that large doses of fish oil must be taken to achieve an antiinflammatory effect. This perception is based on use of fish oil in soft gelatine capsules, which typically contain 1 g of fish oil. The median dose in published trials of fish oil in RA was 10 g per day but many studies employed doses of 15-20 g per day of encapsulated fish oil, of which omega-3 fats make up 30% w/w<sup>2</sup>.

While 15-20 one gram capsules daily is a physically and financially challenging dose, 15-20 ml of oil is not, and bulk (i.e., unencapsulated) fish oil can be taken in required doses inexpensively. Cod liver oil can be used since it typically contains similar proportions of omega-3 fats to standard fish body oils.

Hypervitaminosis A is not a risk at the dose recommended. In Australia, a 20 ml dose of cod liver oil costs about 20 cents per day compared to \$5 for a comparable dose of fish oil capsules. Similar differentials are likely to apply elsewhere. The taste can be minimized with the "two glass technique." This involves adding fish oil without stirring to the surface of fruit or vegetable juice in a small glass. The contents of this glass are swallowed and then followed immediately by fresh juice from a second glass. This fresh juice is moved about the mouth before swallowing to mobilize residual oil that might cause an aftertaste. Taking the dose immediately before a solid meal minimizes repeating of the fish taste.

Considering the foregoing, what dietary advice should one give? We suggest that inexpensive bulk fish oil be tried in the first instance. For those who do not tolerate bulk fish oil or who have an aversion to this idea, fish oil capsules can be used. Capsules are available that contain an omega-3 concentrate from fish oil, reducing the number of capsules required to achieve an antiinflammatory dose, albeit at increased cost. The goal for antiinflammatory therapy should be a daily intake of a total of 3-6 g of the long chain omega-3 fats, EPA, and docosahexaenoic acid (DHA). It should be noted that cardiovascular benefits have been observed at EPA + DHA intakes < 1 g/day<sup>9,10</sup>. Advice can be given to avoid unnecessary intake of competitor omega-6 fats, in which Western diets are hyperabundant. Omega-6 fats are abundant in products based on polyunsaturated vegetable oils such as soy, corn, safflower, sunflower, and others. It is a simple substitution to use products rich in mono-unsaturated oils such as canola and olive in their place. Fresh ground linseed can be added to cereals as a vegetable source of omega-3 fats, albeit in a less potent form than EPA in fish oil. Of course, fish itself is a good source of dietary omega-3 fats but intakes in Western countries fall well below those shown in therapeutic studies to have antiinflammatory effects. Future developments in production of a variety of omega-3 enriched foods is likely to achieve success in increasing omega-3 fat intake because they will provide increased dietary options<sup>15</sup>.

Given the multiple dietary factors that can influence omega-3 fat levels in tissues, a marker for tissue omega-3 fat enrichment should be a useful guide to changes in dietary omega-3 nutrition in response to advice. A target of 3.2% EPA as a percentage of total fatty acids in plasma phospholipids is proposed, as this level corresponds to a mononuclear cell level that is associated with significant inhibition of interleukin 1 and tumor necrosis factor synthesis by these cells *ex vivo*<sup>15,16</sup>. Recent studies from our early arthritis clinic indicate that substantially higher levels can be achieved through the simple measures outlined above and that patients vary considerably in levels achieved (unpublished observations). While the value of this index needs to be evaluated prospectively, it may prove especially useful because of the need to sustain effective dietary supplementation for 2 or more months before clinical benefits can be expected.

What further questions need to be addressed with regard to omega-3 fats in RA? Of considerable interest is the potential for preventive effects of dietary omega-3 fats in RA. Dietary fish oil can have potent preventive effects in mice genetically predisposed to inflammatory disease<sup>17</sup>. Epidemiological studies indicate a relatively low prevalence of RA in Japanese despite a high prevalence of the rheumatoid susceptibility epitope-bearing DRB1

allele 0405<sup>18</sup>. Also, a case-control study of women's health in Seattle showed an inverse correlation between fish ingestion (2 or more fish meals per week) and seropositive RA (odds ratio 0.3)<sup>19</sup>. Thus, introduction of omega-3 fats in the diet may benefit those at risk of RA, such as first degree relatives of RA sufferers and those otherwise predisposed genetically to RA. Conceivably, this risk may be reduced by changes in family food preparation to include more omega-3 fats, and these dietary changes can also be expected to reduce cardiovascular risk.

Other issues that warrant examination include the influence that dietary omega-3 fats may have in regimens for the management of recent onset polyarthritis, in maintenance of remission achieved through early intervention in RA, and in longterm outcome studies in RA.

In summary, based on efficacy and safety data, collateral health benefits, potential to reduce unwanted drug effects, and low cost, dietary fish oil supplements should now be regarded as part of standard therapy for RA. Implementation will be greatly assisted by the production of a greater variety of omega-3 enriched foods than exists currently.

**LESLIE G. CLELAND, MD, FRACP**

Director, Rheumatology Unit,  
Royal Adelaide Hospital, North Terrace,  
Adelaide, Australia 5000;

**MICHAEL J. JAMES, PhD,**

Chief Medical Scientist, Rheumatology Unit,  
Royal Adelaide Hospital.

*Address reprint requests to Dr. Cleland.*

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