Editorial

Marine Oils for Antiinflammatory Effect — Time to Take Stock


SEAL OIL IN PSORIATIC ARTHRITIS

The report in this issue of *The Journal* by Madland and coworkers[1] describes the therapeutic use of seal oil in psoriatic arthritis (PsA). The study fails to achieve its primary endpoints of reduced joint pain and patient global assessment of impact on disease after 2 weeks of treatment. This time period was chosen based on improvement in joint symptoms over this period in an earlier study of seal oil in inflammatory bowel disease[2,3]. The studies differ in that seal oil was given orally in the present study and by intra-duodenal intubation in the earlier study. With duodenal delivery, somewhat higher levels of serum long-chain omega-3 fatty acids (omega-3 fatty acids) were achieved.

PUTATIVE MERITS OF SEAL OIL VS FISH OIL

The authors explain that seal oil differs from fish oil in that its omega-3 fatty acids are found in the sn1 and sn3 positions in triglycerides and not in the sn2 position, their usual location in triglycerides in fish oils and in membrane phospholipids. They argue that this configuration may favor the absorption of long-chain omega-3 fatty acids from seal oil. However, absorption of long-chain omega-3 fatty acids from fish oil is normally efficient and, in the absence of direct evidence, the notion that omega-3 fatty acids are more bioavailable in seal oil than fish oil is not compelling, particularly in the absence of bowel inflammation sufficient to compromise fat absorption. In addition, the benefit of putative "rapid absorption" of omega-3 fatty acids from seal oil appears to have little relevance for a treatment strategy that is longterm in nature, as discussed below. Indeed, the serum levels of omega-3 fatty acids achieved in the present study were 6.6% w/w of total fatty acids after 2 weeks' treatment with seal oil that provided 6.1 g omega-3 fatty acids per day. These levels are less than half those achieved in plasma in a one-month study of healthy subjects ingesting 5.5 g omega-3 fatty acids per day as Maxepa fish oil. Broadly similar findings were obtained with 2 other brands of fish oil[4].

LATENCY OF SYMPTOMATIC BENEFIT

There have been no previous studies of marine oil in PsA and, to date, most studies have focused on use of fish oil in rheumatoid arthritis (RA)[5]. The symptomatic benefit seen with fish oil in RA is thought to be related to inhibition of synthesis of nociceptive prostaglandin E_2 (PGE_2) through competitive inhibition of metabolism of arachidonic acid (AA) by cyclooxygenase (COX) by the long-chain omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). This symptomatic effect of fish oil lacks the immediacy of the analgesic response to nonsteroidal antiinflammatory drugs (NSAID) and there is generally a latency of 6 to 12 weeks between commencing antiinflammatory doses of fish oil and symptomatic improvement[5]. There is no reason to believe this should be different with seal oil and the present study serves as a reminder that treatment of inflammatory diseases with marine oils rich in long-chain omega-3 fatty acids is a longterm, not a short-term, management strategy.

ADVANTAGES OF FISH OILS OVER NSAID

While not suitable for on-demand use, fish oils have a number of advantages over NSAID. First, they have not been associated with serious upper gastrointestinal complications. Second, they have been shown to reduce risk for cardiovascular events, including cardiac death, through multiple actions (see below)[6]. This benefit contrasts with the increased cardiovascular risk seen with NSAID, as identified first with COX-2 selective agents and more recently linked to NSAID more generally[7,8]. Third, fish oils have been shown to reduce synthesis of the proinflammatory cytokines tumor necrosis factor (TNF) and interleukin 1 (IL-1) by mononuclear cells[9], in contrast to NSAID, which can increase synthesis of these cytokines[10]. Thus, the 50% reduction in discretionary NSAID use seen with fish oil treatment in RA is clearly an advantage[11]. This NSAID-sparing effect is especially important as some authorities are now recommending that NSAID be used in doses as

See Subjective improvement in patients with PsA after short-term oral treatment with seal oil, *page 307*

small and for periods as short as are required[12]. Thus longterm fish oil treatment may reduce NSAID use and reduce gastrointestinal and cardiovascular events in potential longterm NSAID users. These advantages may conceivably apply to seal oil, for which very few data are available. Further, the effects of fish oil in the maintenance of remission in Crohn's disease[13] and suppression of disease progression in IgA nephropathy[14] suggest a disease modifying potential not seen with NSAID.

CONTRAST BETWEEN NSAID AND OMEGA-3 FATTY ACIDS FOR EFFECTS ON COX-DERIVED EICOSANOIDS

The safety profile of the omega-3 fatty acids in the fish oil, like the risk profile of NSAID, can be largely explained by their unique effects on eicosanoid synthesis. EPA, for example, is a natural homolog of AA, with a structural difference of only one additional double bond (the omega-3 bond) and not surprisingly, it is an alternative substrate and inhibitor of AA metabolism by COX. EPA and DHA inhibit the activity of both COX-1 and COX-2 with a K_i of approximately 2 μM, which is similar to that for ibuprofen[15]. When long-chain fatty acids are released from cell membranes, the COX isozymes are the immediate enzymes in the pathway of fatty acid metabolism to eicosanoids. Within the context of Western dietary habits, AA is the major COX substrate and prostaglandin H_2 (PGH_2) its immediate product. PGH_2 is converted by respective terminal synthases to PGE_2, thromboxane A_2 (TXA_2), and prostacyclin (PGI_2). The balance of TXA_2, a vasoconstrictor and promoter of platelet aggregation, and PGI_2, a vasodilator and inhibitor of platelet aggregation, is critical for vascular/platelet homeostasis and atherogenesis[16,17].

Whereas PGH_2 is the COX metabolite of AA, PGH_3 is the COX metabolite of EPA. Studies of prostanoid metabolism in the presence of dietary EPA or exogenous EPA added *in vitro* suggest PGH_3 is a poor substrate and an inhibitor of PGE synthases[18] and TXA synthase[19] and a potential substrate without inhibitory effect on PGI synthase[20]. Indeed, the increased PGI_2 synthesis seen with antiinflammatory doses of fish raises the possibility of "shunting" of PGH_2 from blocked PGE synthase and TX synthase to uninhibited PGI synthase[20]. Thus, the overall effect of EPA is suppression of PGE_2 synthesis and shifting of the TXA_2/PGI_2 balance in favor of PGI_2. This contrasts with the effects of selective COX-2 inhibitors, which shift the TXA_2/PGI_2 balance in favor of TXA_2 [21,22]. A likely mechanism for this NSAID effect lies in the different enzyme kinetic characteristics of PGI synthase compared with TXA synthase[23]. TX synthase has a higher initial reaction velocity, but is saturated at a lower concentration of PGH_2 substrate compared with PGI synthase[23]. Thus, when total COX activity is partially inhibited, as occurs with selective COX-2 inhibition or with all NSAID at certain doses, PGH_2 concentration is reduced to an extent that reduces PGI_2 synthesis with little or no effect on TXA_2 synthesis.

CARDIOVASCULAR BENEFITS

The cardiovascular benefits of dietary enrichment with omega-3 fatty acids are substantial and include a moderate hypotensive effect[24] (possibly prostacyclin-mediated and opposite to the hypertensive effects of NSAID), anti-arrhythmic actions[25,26], reduced arterial stiffness[27], reduced C-reactive protein[28], inhibition of TNF and IL-1 synthesis[9] (implicated in atheroma), improved blood lipid profile[29] (reduced triglycerides, increase in HDL cholesterol), and most importantly, reduced overall mortality[28]. The latter effect compared favorably with statins in metaanalysis of the large, longterm randomized trials of antilipemic therapies[30].

ADVERSE EFFECTS OF MARINE OILS

Based on toxicological, population, case control, and clinical studies, it seems unlikely unwanted effects will arise from an excess of constituent omega-3 fatty acids. Recently, attention has been drawn to the adverse effects of mercuric compounds that accumulate in long-lived fish[31]. Fortunately, mercury does not accumulate in fat and can be removed during processing of marine oils, and levels can be readily monitored. Another class of contaminants to consider are dioxins and dioxin-like polychlorobiphenyls (PCB). These industrial pollutants, which also contaminate the terrestrial food chain, accumulate in body fat and milk. Current levels of intake in Australasia are assessed as very low, but intakes may be higher in other locations[32]. Antiinflammatory doses (200 mg/kg/day) of fish oil did not increase intakes beyond acceptable levels. However, content within fish oil products can vary[33]. These contaminants can be reduced by processing and in general, levels in products have fallen over the last decade. Since variability between products has been shown to exist, more stringent measures of analysis of the most relevant congenors are being introduced. As seals are sea mammals atop the marine food chain, seal oil may warrant special attention in this regard.

INDUSTRY MARKETING AND ENGAGEMENT OF PRESCRIBERS

In conclusion, the benefit/risk profile for longterm use of omega-3-rich marine oils in inflammatory or cardiovascular disease far outweighs that for NSAID. However, there is a considerable mismatch in their use, with widespread routine prescription of NSAID and neglect of fish oils by prescribers. This mismatch says a great deal about the influence of pharmaceutical company marketing. The latter is enabled by the extraordinary profit margins of the industry and is delivered by clinical opinion leaders, who use their product "advisory" relationships with companies to support travel and professional networking habits[34]. Ironically, rather than more evidence of benefit, which is already ample, a future

need will be for larger-scale, sustainable production of omega-3 fatty acids free of environmental pollutants. This might be achieved through plant and microorganism production and may provide the type of product and market conditions that can stimulate the commercial marketing required for broader prescriber engagement.

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