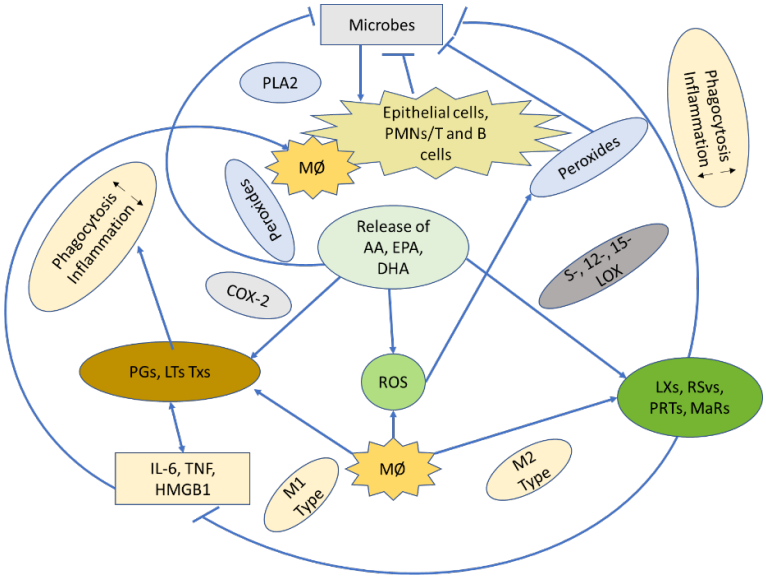
COVID-19, Bioactive Lipids, and a Potential Role for Icosapent Ethyl (VASCEPA®)

The COVID-19 pandemic is unlike anything we have seen in our lifetimes. It has created an unprecedented healthcare crisis. Scientific leaders and Amarin believe that icosapent ethyl (VASCEPA®) should be studied in the context of COVID-19 based on the drug's established safety and efficacy profile, and due to its potential anti-inflammatory, anti-thrombotic, and anti-viral effects that could be useful to alter the natural history of COVID-19. Early data from China reveals that the case fatality rate from COVID-19, 0.9% for patients with no comorbidities, is significantly increased to 10.5% for patients with cardiovascular disease.[1] Icosapent ethyl is generally a safe medication that has been shown to have significant cardiovascular benefits in the REDUCE-IT® trial. In addition to such benefits with chronic dosing, icosapent ethyl has rapid plasma uptake with acute dosing, and there is evidence for long-chain polyunsaturated fatty acids such as EPA (eicosapentaenoic acid) having anti-viral effects. As the company that produces this drug, Amarin is willing to collaborate in clinical research involving randomized assessment. Please see below for a quick summary of the scientific rationale. There is broad enthusiasm among investigators to study this compound in the backdrop of COVID-19 patient management.

An article entitled, *Can Bioactive Lipids Inactivate Coronavirus (COVID-19)?*,[2] in Archives of Medical Research, notes that polyunsaturated fatty acids and their metabolites (bioactive lipids) inactivate enveloped viruses, possess anti-inflammatory and wound healing actions, and release arachidonic acid (AA) and other unsaturated fatty acids into their surrounding milieu when challenged by various microorganisms including viruses such as SARS-CoV-2, SARS, and MERS. In turn, these polyunsaturated fatty acids and their metabolites inactivate such invading organisms and, thus, protect lungs and other tissues.

The author notes that the downstream effects of prostaglandins, leukotrienes, and thromboxanes formed from AA have pro-inflammatory actions whereas lipoxins (from AA), resolvins from EPA (eicosapentaenoic acid, 20:5 n-3) and DHA (docosahexaenoic acid, 22:6 n-3), and protectins and maresins (derived from DHA) have potent anti-inflammatory actions, resolve inflammation and aid in wound healing and at the same time augment phagocytic capacity of macrophages and other cells to help remove debris from the site(s) of infection and injury and enhance microbial clearance (Figure 1).[2]

Figure 1.



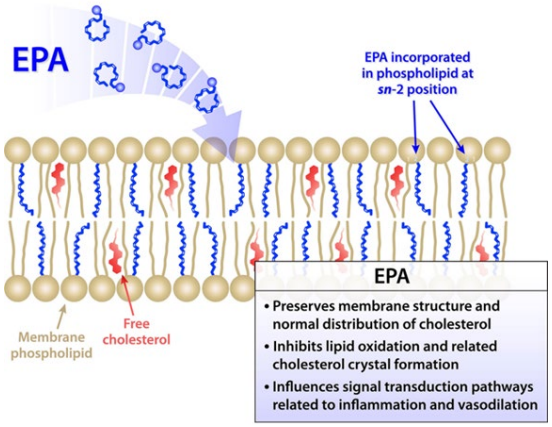
Scheme showing how bioactive lipids could inhibit microbial proliferation.
Adapted from Das U. *Archives of Medical Research*, in-press 2020

Because SARS-CoV-2 is an enveloped virus, the author proposes that oral or intravenous administration of unsaturated fatty acids may aid prevention of, or recovery from, these infections and, when present in adequate amounts in immunocytes and body fluids (especially in the alveolar fluid), may decrease morbidity and mortality of the current pandemic (Figure 1).[2]

Icosapent Ethyl (EPA Ethyl Ester) and EPA Reduce Inflammation

In the REDUCE-IT cardiovascular outcomes trial icosapent ethyl at 4 grams daily demonstrated robust and consistent reductions in cardiovascular risk in statin-treated patients across multiple endpoints and subgroups.[3] Icosapent ethyl also demonstrated a favorable safety profile and, based on the REDUCE-IT results, is currently approved in the United States and Canada and is under regulatory review in Europe, with additional regulatory approvals being pursued in China and the Middle East. While the mechanistic effects are not fully understood, and cannot be explained solely by mechanisms such as triglyceride lowering, it is suggested that efficacy is due at least in part to EPA's role as a bioactive lipid that preserves membrane structure and normal distribution of cholesterol, inhibits lipid oxidation and cholesterol crystal formation, influences signal transduction pathways associated with inflammation and vasodilation, and involves transcriptional regulation of multiple related genetic pathways (Figure 2).[4]

Figure 2.



Mason RP, Libby P, Bhatt DL. *Arteriosclerosis, Thrombosis, and Vascular Biology,* 2020

Anti-inflammatory effects of EPA may stem in part from competitive displacement of AA in membrane phospholipids, as AA in phospholipids is metabolized into pro-inflammatory lipid mediators such as prostaglandins and thromboxanes.[5] When substituted for AA, EPA is metabolized by lipoxygenases and cyclooxygenases into five (5) series leukotrienes, which have diminished inflammatory effects, as well as other mediators, such as resolvins, that modulate resolution of the inflammatory response.[6]

Relevant to the acute needs and rapid therapeutic timing in the care of COVID-19 patients, pharmacokinetic studies have shown that, following icosapent ethyl dosing, maximum concentration of total EPA was reached in approximately five to six (5-6) hours in plasma and approximately eight (8) to 24 hours in red blood cells (a marker of peripheral tissue uptake). The mean terminal half-life of total EPA in plasma was long, ranging between 70 and 89 hours[7]

In clinical studies of patients, EPA-only treatment has been reported to reduce high-sensitivity C-reactive protein, lipoprotein-associated phospholipase A2, and oxidized LDL-C levels, the AA-to-EPA ratio,[8] soluble intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1),[9] and interleukin 10 (IL-10), an anti-inflammatory cytokine involved in macrophage recruitment that contributes to reducing inflammation and improving the insulin signal.[10] EPA has also been shown to increase adiponectin, an adipocytokine with anti-inflammatory and anti-atherogenic properties.[11]

In cellular studies, among many studies that corroborate EPA's anti-inflammatory effects, EPA reduced production of inflammatory mediators such as tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β) compared to another long-chain polyunsaturated fatty acid, docosahexaenoic acid (DHA), in alveolar macrophages following lipopolysaccharide stimulation.[12]

Specific to sepsis, a recent systematic analysis found that omega-3 fatty acid supplementation could reduce the mortality rate of sepsis and sepsis-induced acute respiratory distress syndrome (ARDS) in adults and suggests that further investigation based on suitable concentrations and indications is needed to support the findings.[13]

Further, in an animal model, EPA treatment exerted a strong resistance to sepsis defined by the absence or delay of inflammation. The authors propose that EPA preconditioned the heart against septic damage through several modifications that protect mitochondrial integrity, attributing the effect to reduced early-stage reactive oxygen species insult to mitochondria, which is a precursor to detectible reductions in cardiac mechanical function. Therefore, EPA demonstrated potential upstream benefits before cardiac damage, which is hypothesized to be related to increased uncoupling protein-3 (UCP3) and sirtuin-3 (SIRT3) expression that precondition the myocardium to better handle the eventual sepsis insult.[14]

Cardiovascular Risk and COVID-19

Patients who have multiple cardiovascular and respiratory risk factors are understood to be at higher risk for not surviving COVID-19. In the REDUCE-IT cardiovascular outcomes trial icosapent ethyl at 4 grams daily demonstrated robust and consistent reductions in cardiovascular risk in statin-treated patients across multiple endpoints and subgroups. Even if icosapent ethyl does not directly impact the virus, appropriate patients treated with icosapent ethyl may lower their risk of COVID-19 complications by lowering their cardiovascular risk.

Summary

While not studied in a large, randomized outcome study in patients infected with COVID-19, there are substantial preclinical and clinical data from Amarin studies to suggest that the active ingredient in Vascepa has potential anti-inflammatory, anti-thrombotic, and anti-viral properties, which ultimately may result in beneficial effects within those infected patients. And, VASCEPA may lower patient risk of COVID-19 complications by lowering their cardiovascular risk. These potential biological effects in the backdrop of COVID-19 deserve further study, including in randomized clinical trials.

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