

Title: Parenteral fish oil, an adjuvant pharmacotherapy for COVID-19?

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Abstract

The new coronavirus 2 associated to severe acute respiratory syndrome (SARS-CoV-2), surprisingly, does not affect only the lung. The severe response to SARS-CoV-2 appears to include a “cytokine storm”, which indicates a state of hyperinflammation and subsequent dysfunction of multiple organs and tissues in the most severe cases. This could be the reason why populations at highest risk of death from the SARS-CoV-2 infection-induced disease (COVID-19) are those suffering from chronic low-grade inflammation, but prone to hyperinflammation - advanced age, obesity, type 2 diabetes, hypertension and metabolic syndrome. Inflammation resolution is strongly dependent on lipid mediators, the specialized pro-resolution mediators (SPMs). Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are precursors of very potent SPMs, including resolvins, protectins and maresins. In addition, they are associated with a less aggressive inflammatory initiation, after competing with omega-6 fatty acids for eicosanoid synthesis. Therefore, it makes sense to consider the use of n-3 PUFAs for clinical management of COVID-19 patients. N-3 PUFAs may be given by oral, enteral or parenteral routes, but the parenteral route favors their faster incorporation into plasma phospholipids, blood cells and tissues. Here, we discuss these aspects to propose the parenteral infusion of n-3 PUFAs as an adjuvant immunopharmacotherapy for hospitalized patients with COVID-19.

Key words: COVID-19; Hyperinflammation; Resolution of inflammation; Specialized pro-resolving mediators; Parenteral fish oil

Hypothesis

COVID-19 - Coronavirus Disease 2019 – is caused by coronavirus 2 associated to severe acute respiratory syndrome (SARS-CoV-2), a virus that emerged in 2019. The first cases described begun in December 2019, in the Wuhan (Hubei province in China), as a pneumonia of unknown etiology.¹ Four months later 167 countries and territories had already registered 2.074.529 confirmed infected patients and 139.378 deaths.²

However, COVID-19 mortality may go beyond compromising of the lungs. Initial reports suggest that 14% of patients fulfill severity criteria that besides respiratory failure include circulatory shock and/or multiple organs and systems dysfunction accompanied by ischemia of the fingers and toes.³ In a Dutch ICU, from 184 COVID-19 patients, 38% were reported to have abnormal blood clotting and 33% with identified clots.⁴ Blood clots may cause lung emboli or stroke. In addition, populations with high risk to develop the more severe forms of COVID-19 do not necessarily include patients with respiratory diseases, as expected, but patients with advanced age, obesity, diabetes, hypertension and metabolic syndrome.³ These patients share a common characteristic: all can have alterations favoring hyperinflammation (low grade chronic inflammation) and compromise of inflammatory resolution.⁵⁻⁹ The persistent inflammation found in these types of patients may be considered a predisposing factor to thrombosis.¹⁰ Other features common to these conditions may be involved such as poor glucose control and hyperglycemia. In the context of our hypothesis it is important to note that elevated blood glucose may itself create a state of hyperinflammation.¹¹ In fact, the driving force behind the clinical decline in many of severely ill COVID-

19 patients could be an exaggerated and disastrous reaction of the immunologic system, termed a “cytokine storm” known to occur after other viral infections.³

When SARS-CoV-2 infects the superior and inferior respiratory tract, it may cause acute respiratory distress syndrome (ARDS) through mechanisms that seem to engage activation of a cascade of inflammation in the inferior respiratory tract.¹² A cytokine profile similar to secondary hemophagocytic lymphohistiocytosis is associated with COVID-19 severity as well as high levels of ferritin and interleukin 6 (IL-6), considered mortality predictors.¹³ This may indicate a hyperinflammation unleashed by the viremia.

Cytokines are protein molecules signaling pro- and anti-inflammatory responses that in a balanced situation contribute to a healthy immunological response. However, in a situation of cytokine storm the pro-inflammatory cytokine levels increase much more than necessary and immune cells start to attack healthy tissues. This can result in blood vessel leakage, arterial pressure fall, clot formation and organ failure.¹⁴

Cytokine production is part of the natural physiologic inflammatory response and exacerbated production may suggest a deficiency of the resolution response. The inflammatory resolution process is different from familiar immunological response characterized by fever, redness, and edema. Inflammation resolution involves participation of some anti-inflammatory cytokines, mainly IL-10, but it is mainly controlled by a group of molecules called specialized pro-resolution mediators, or SPMs.¹⁵

SPMs are distinct from many other immunologic signaling molecules, in composition – they are lipids and not proteins – and in their action. While pro-

inflammatory protein mediators are highly involved in activating immune cells for identification and destruction of invasive organisms, SPMs accelerate the cleaning process and tissue regeneration, allowing homeostasis to return.¹⁶

Many lipid immune mediators, like SPMs, are synthesized from long chain polyunsaturated fatty acids (PUFAs). These PUFAs include arachidonic acid (ARA), from the omega-6 (n-6) family, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both from omega-3 (n-3) family. Lipid mediators generated from these PUFAs may participate in both activation and resolution of the inflammatory response.¹⁷

EPA and ARA compete for the lipoxygenase (LOX) and cyclooxygenase (COX) pathways for synthesis of eicosanoids, lipid mediators typically involved in inflammation activation.¹⁷ While ARA is the precursor for pro-inflammatory eicosanoids, also known to be immunosuppressive and thrombotic, EPA generates eicosanoids that are less functionally intense and anti-thrombotic. For example, leukotriene B₅, which is EPA derived, has a chemotactic potential 10 to 30 times less potent on neutrophils than leukotriene B₄ derived from ARA.¹⁸ Therefore, responses with EPA as substrate for eicosanoid synthesis have less pro-inflammatory potential than those with ARA as substrate.

In addition, both EPA and DHA are precursors of resolvins and DHA is the precursor of protectins and maresins – all SPMs. Resolvins and protectins are liberated during cell-to-cell communication during the inflammation resolution phase, via transcellular biosynthesis and they participate in regulation and resolution of inflammation.¹⁶⁻²² Maresins are conjugates of sulfides synthesized by macrophages, which are also

participants in acute inflammation resolution and seem to promote tissue regeneration.²³ Maresin 1 biosynthesis involves an active intermediate (13S,14S-epoxi-DHA) that stimulates macrophage conversion from M1 (pro-inflammatory) to M2 (anti-inflammatory) phenotype.²⁴

Thanks to their specific properties, resolvins, protectins and maresins from n-3 PUFAs can inhibit polymorphonuclear leukocyte activation and stimulate the recruitment of non-inflammatory leukocytes, that eliminate remnants from neutrophil apoptosis (efferocytosis). These SPMs also participate in pro-inflammatory cytokine “kidnapping” and removal of other remnants (such as invasive microorganisms residues) providing restoration of normal structure and tissue homeostasis.¹⁹⁻²³ With their action of contra-regulation of pro-inflammatory mediators, SPMs have been shown to decrease inflammation magnitude and duration, and stimulate re-epithelization, wound healing and tissue regeneration in experimental models.²⁵

It is worth noting that EPA and DHA also may to inhibit the synthesis of pro-inflammatory cytokines by modulating the activation of gene transcription factors, such as the nuclear factor kappa B (NF κ B) and the peroxisome proliferator activated receptor (PPAR), and destabilizing membrane lipid *rafts*. PPAR activation by agonists was proposed as a therapeutic target for cytokine storm modulation in COVID-19 and may be supported by n-3 PUFAs.²⁶ Furthermore, the angiotensin-converting enzyme 2 (ACE2), a receptor used by the SARS-CoV-2 to entry in human cells, is located at membrane lipid *rafts*.²⁷

About 5% of COVID-19 patients may need ICU treatment, usually

requiring ventilator support and two-thirds of these may fulfill the criteria for ARDS. According to a study done in Wuhan, over half of the hospitalized adult patients who died (27/54) also had a secondary infection.²⁸

In ARDS patients, the enteral use of n-3 PUFAs has been associated to oxygenation improvement, reduced duration of mechanic ventilation as well as shorter ICU length of stay.²⁹ Critically ill patients receiving parenteral nutrition therapy enriched with fish oil lipid emulsion (rich in n-3 PUFAs EPA and DHA) were reported to have decreased infection and sepsis risk (40% to 56%, respectively) and a reduction of length of hospital and ICU stay by about two days.³⁰

For the moment, while there is not a specific treatment for SARS-CoV-2 infection, clinical management includes a conservative strategy in intravenous fluid administration, early empiric antibiotic therapy to treat a possible associated bacterial infection, anti-coagulants, early preventive pulmonary ventilation, periodic pronation during mechanic ventilation and oxygenation by extra-corporeal membrane, when required.³¹ Despite these efforts, COVID-19 mortality rate may, in some situations be almost 50%. One possible explanation would be an apparent antibiotic resistance. In the already quoted Wuhan study, where half of the patients who died had a secondary infection, all, except one, had been treated with antibiotics.²⁸ Anti-inflammatory drugs use for COVID-19 ARDS is disputed, because there may be a risk of infection worsening and an increase of secondary infections due to immunosuppression.³

Of note, SPMs produced from metabolism of n-3 PUFAs are different from the anti-inflammatory drugs currently available. While they decrease pro-

inflammatory mediator synthesis and neutrophil recruitment, they activate macrophages with an anti-inflammatory phenotype (M2) and stimulate phagocytosis in a non-phlogistic manner.³² Therefore it makes sense to consider the use of n-3 PUFAs in the clinical management of COVID-19 patients.

N-3 PUFAs may be given by oral, enteral or parenteral routes. However, they are incorporated in plasma phospholipids and blood cells more rapidly when infused intravenously (1-3 days), than when given orally or enterally (4-7 days).³³ For instance, significant accumulation of EPA in blood white cells occurs within 1 or 2 days of infusion and alterations in blood cytokine levels occur over a time frame of 3 days.^{34,35} Besides that, parenteral infusion of n-3 PUFAs avoids the inevitable losses due to disruption of the digestive and absorptive processes (described in COVID-19 patients) after their enteral intake. In clinical practice, the parenteral provision of n-3 PUFAs is through the infusion of a lipid emulsion (LE) compounded by pure fish oils (LEFO) or lipid emulsions containing fish oil combined with other lipids (soybean oil, olive oil, and medium chain triglycerides) already available worldwide.¹⁷

LEs are an integral part of parenteral nutrition therapy, but the sole intravenous infusion of LEFO (0.1-0.2 g fat/bw/d) has been proposed to some patients without indication for parenteral nutrition as an immune-pharmac-nutrient. The infusion of LEFO was in our experience safe and without direct adverse effects.³⁶ We found that in digestive cancer patients, this practice has been associated with post-operative attenuation of inflammatory mediators and leukocyte functions.³⁶ Other investigators also found this practice safe

and beneficial in critically ill patients with sepsis and general elderly critically ill patients. In the septic populations, benefits included anti-inflammatory and hepatoprotective effects, general reduction in organ dysfunction and a reduction in mortality restricted to patients with less severe sepsis.^{37,38} In the elderly populations, detrimental plasma PUFA profiles were observed, which were attenuated by LEFO and resulted in better inflammatory response and gas exchange, contributing to survival.^{35,39}

The intravenous infusion of LEFO allows that bioactive n-3 PUFAs become available immediately to cells and tissues to exert their anti-inflammatory and tissue reparative properties. We propose to consider the parenteral infusion of LEFO as an adjuvant pharmacotherapy at the hospitalization of COVID-19 patients until 14 days³⁶ or their clinical recovery, aiming to attenuate respiratory failure and reduce infection and sepsis rate, as well as length of stay at ICU and hospital. This proposal is supported by sound experimental and clinical evidence, even in patients suffering from ARDS.^{29,30}

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