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Parenteral fish oil: An adjuvant pharmacotherapy for coronavirus disease 2019?

Raquel S. Torrinhas Ph.D. [a,*], Philip C. Calder Ph.D. [b,c], Gabriela O. Lemos GCert [a], Dan L. Waitzberg Ph.D. [a]

[a] Department of Gastroenterology, Faculty of Medicine, Laboratory of Nutrition and Metabolic Surgery, University of São Paulo, São Paulo, Brazil
[b] Human Development & Health, Faculty of Medicine, University of Southampton, Southampton, United Kingdom
[c] NIHR Southampton Biomedical Research Center, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, United Kingdom

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ABSTRACT

The new coronavirus associated with severe acute respiratory syndrome (SARS-CoV-2), surprisingly, does not affect only the lungs. 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 the highest risk for death from the SARS-CoV-2 infection–induced disease (coronavirus disease 2019 [COVID-19]) are those suffering from chronic low-grade inflammation, but prone to hyperinflammation. This includes individuals of advanced age and those with obesity, type 2 diabetes, hypertension, and metabolic syndrome. Inflammation resolution is strongly dependent on lipid mediators, the specialized pro-resolution mediators (SPMs). ω-3 polyunsaturated fatty acids (ω-3 PUFAs) are precursors of very potent SPMs, including resolvins, protectins, and maresins. Additionally, they are associated with a less aggressive inflammatory initiation, after competing with ω-6 fatty acids for eicosanoid synthesis. Therefore, it makes sense to consider the use of ω-3 PUFAs for clinical management of COVID-19 patients. ω-3 PUFAs may be given by oral, enteral, or parenteral routes; however, the parenteral route favors faster incorporation into plasma phospholipids, blood cells, and tissues. Here, we discuss these aspects to propose the parenteral infusion of ω-3 PUFAs as adjuvant immunopharmacotherapy for hospitalized patients with COVID-19.

Hypothesis

Coronavirus disease 2019 (COVID-19) is caused by coronavirus 2 associated with severe acute respiratory syndrome (SARS-CoV-2), a virus that emerged in 2019. The first cases described began 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 million confirmed infected patients and 139 378 deaths [2].

However, COVID-19 mortality may go beyond compromising the lungs. Initial reports suggest that 14% of patients fulfill severity criteria that, in addition to respiratory failure, include circulatory shock and/or multiple organs and system dysfunction accompanied by ischemia of the fingers and toes [3]. Of 184 patients with COVID-19 in a Dutch intensive care unit (ICU), 38% were reported to have abnormal blood clotting and 33% had identified clots [4]. Blood clots may cause lung emboli or stroke. Additionally, populations with a high risk for developing the more severe forms of COVID-19 do not necessarily include patients with respiratory diseases, as expected, but rather those with advanced age, obesity, diabetes, hypertension, or 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 patients may be considered a predisposing factor to thrombosis [10]. Other features common to these conditions may be poor glucose control and hyperglycemia. In the context of the present 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 the severely ill patients with COVID-19 could be an exaggerated and disastrous reaction of the immunology system, termed a *cytokine storm*, which is 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)

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*Corresponding author: Tel.: +55 3061 7459.
E-mail address: rtorrinhas@gmail.com (R.S. Torrinhas).

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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 (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 immunologic response. However, in a situation of cytokine storm, the proinflammatory cytokine levels increase much more than necessary and the immune cells start to attack healthy tissues, which can result in blood vessel leakage, a decrease in arterial pressure, 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 immunologic 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* (SPMs) [15].

SPMs are distinct from many other immunologic signaling molecules, in composition—they are lipids and not proteins—and in their action. Although proinflammatory 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 ω-6 family, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), both from the ω-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 and cyclooxygenase pathways for synthesis of eicosanoids, lipid mediators typically involved in inflammation activation [17]. Whereas ARA is the precursor for proinflammatory eicosanoids, also known to be immunosuppressive and thrombotic, EPA generates eicosanoids that are less functionally intense and antithrombotic. For example, leukotriene B_5, which is EPA-derived, has a chemotactic potential 10 to 30 times less potent on neutrophils than leukotriene B_4 derived from ARA [18]. Therefore, responses with EPA as substrate for eicosanoid synthesis have less proinflammatory potential than those with ARA as substrate.

Additionally, 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 synthetized by macrophages, which also are participants in acute inflammation resolution and seem to promote tissue regeneration [23]. Maresin 1 biosynthesis involves an active intermediate (13 S,14 S-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 ω-3 PUFAs can inhibit polymorphonuclear leukocyte activation and stimulate the recruitment of non-inflammatory leukocytes, which eliminate remnants from neutrophil apoptosis (efferocytosis). These SPMs also participate in proinflammatory 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 proinflammatory mediators, SPMs have been shown to decrease inflammation magnitude and duration, and stimulate reepithelization, wound healing, and tissue regeneration in experimental models [25].

It is worth noting that EPA and DHA also may to inhibit the synthesis of proinflammatory cytokines by modulating the activation of gene transcription factors, such as the nuclear factor (NF)κB and the peroxisome proliferator-activated receptor, and destabilizing membrane lipid rafts. Peroxisome proliferator-activated receptor 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, a receptor used by the SARS-CoV-2 to entry in human cells, is located at membrane lipid rafts [27].

About 5% of patients with COVID-19 may need ICU treatment, usually requiring ventilator support. Two-thirds of these patients may meet the criteria for ARDS. According to a study done in Wuhan, >50% of the hospitalized adult patients who died (27 of 54) also had a secondary infection [28].

In patients with ARDS, the enteral use of ω-3 PUFAs has been associated to improve oxygenation, reduce duration of mechanic ventilation, and reduce ICU length of stay (LOS) [29]. Critically ill patients receiving parenteral nutrition therapy enriched with fish oil lipid emulsion (rich in ω-3 PUFAs EPA and DHA) were reported to have decreased infection and sepsis risk (40%–56%, respectively) and a reduction of hospital and ICU LOS by about 2 d [30].

For the moment, although there is no specific treatment for SARS-CoV-2 infection, clinical management includes a conservative strategy in intravenous (IV) fluid administration, early empirical antibiotic therapy to treat a possible associated bacterial infection, anticoagulants, early preventive pulmonary ventilation, periodic pronation during mechanic ventilation and oxygenation by extracorporeal 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]. The use of anti-inflammatory drugs for COVID-19 ARDS is disputed because there may be a risk for infection worsening and an increase of secondary infections as a result of immunosuppression [3].

Of note, SPMs produced from metabolism of ω-3 PUFAs are different from the anti-inflammatory drugs currently available. Although they decrease proinflammatory 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 ω-3 PUFAs in the clinical management of patients with COVID-19.

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

LEs are an integral part of parenteral nutrition therapy, but the sole IV infusion of daily LEFO (0.1–0.2 g fat/bw) has been proposed to some patients without indication for parenteral nutrition as an immunopharmaco-nutrient. The infusion of LEFO was, in our experience, safe and without direct adverse effects [36]. We found that in patients with digestive cancer, this practice has been associated with postoperative 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 IV infusion of LEFO allows that bioactive ω-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 for patients hospitalized with COVID-19 for up to 14 d [36] or their clinical recovery, aiming to attenuate respiratory failure and reduce infection and sepsis rate, as well as ICU and hospital LOS. This proposal is supported by sound experimental and clinical evidence, even in patients with ARDS [29,30].

Declaration of Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Credit author statement

All the authors have substantially contributed to the manuscript's writing, revised it critically, approved it final version and agree to be fully accountable for ensuring the integrity and accuracy of the information there provided.

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