Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
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 GCerta, 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 NHRI Southampton Biomedical Research Center, University Hospital Southampton NHS Foundation Trust and University of Southampton, Southampton, United Kingdom

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 inflammation) and compromise of inflammation 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)
long-chain polyunsaturated fatty acids (PUFAs). These PUFAs [16]. destruction of invasive organisms, SPMs accelerate the cleaning their action. Although proin... 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 (NFκB) 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 mechanical 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.

References

[1] World Health Organization. Novel Coronavirus (2019-nCoV) WHO Bulletin Situ- ation Report - 1. Available at: https://www.who.int/docs/default-source/corona- virus/situation-reports/20200121-sitrep-1-2019-ncov.pdf. Accessed April 23, 2020.
[2] World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report - 88. Available at: https://reliefweb.int/sites/reliefweb.int/files/resourc es/20200417-sitrep-88-covid-19166ccd9f48b4f2193777b0f5719a6ed.pdf. Accessed April 23, 2020.
[3] Science. Biology-Coronavirus. How does coronavirus kill? Clinicians trace a ferocious rampage through body-brain-toes. Accessed April 23, 2020.
[4] Klok FA, Krup MJHA, van der Meer NJM, Airbous MS, Gommers DAMP, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;10:50049–3488(2020)31020–1.
[5] Lawrence T, Gilroy DW. Chronic inflammation: a failure of resolution? Int J Exp Pathol 2007;88:85–94.
[6] Goldstein DR, Aging. imbalanced inflammation and viral infection. Virulence 2010;1:295–8.
[7] Bruininga H, Pedersen BK. Age-related inflammatory cytokines and disease. Immunol Allergy Clin North Am 2003;23:15–31.
[8] Ferrucci L, Corsi A, Lauretani F, Bandinelli S, Bartali B, Taub DD, et al. The origins of age-related proinflammatory state. Blood 2005;105:2294–9.
[9] Rius B, López-Vicario C, González-Pérez A, Morán-Salvador E, García-Alonso V, et al. Resolution of inflammation in obesity-induced liver disease. Front Immunol 2012;3:257.
[10] Faioni EM, Edjlali-Goujon M. Inflammation and thrombosis—brothers in arms. Eur Oncol Haematol 2011;7:81–4.
[11] Calder PC, Dimitriadis G, Newsholme P. Glucose metabolism in lymphoid and inflammatory cells and tissues. Curr Opin Clin Nutr Metab Care 2007;10:531–40.
[12] Bahl FA, Al Zoubi MS, Kazabani GA, Salameh DM, Al-Nasser AD. SARS-CoV-2 and Coronavirus Disease 2019: what we know so far. Pathogens 2020;9:E231.
[13] Mehta P, McCulley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. HLH Across Specialty Collaboration, UK. COVID-19: consider cytokine storm syn- dromes and immunosuppression. Lancet 2020;395:1031–4.
[14] Behrens EM, Koretzky GA. Review: cytokine storm syndrome: looking toward the precision medicine era. Arthritis Rheumatol 2017;69:1135–43.
[15] Fullerton JN, Gilroy DW. Resolution of inflammation: a new therapeutic fron- ter. Nat Rev Drug Discov 2009;8:551–67.
[16] Bannenberg GL, Chiang N, Arienti A, Arita M, Tjonabhen E, Gottinger KH, et al. Molecular circuits of resolution: formation and actions of resolutions and protec- tins. J Immunol 2005;174:4345–55.
[17] Watzberg DL, Torrinhas RS. Fish oil lipid emulsions and immune response: what clinicians need to know. Nutr Clin Pract 2009;24:487–99.
[18] Strasser T, Fischer S, Weber PC. Leukotriene B4 is formed in human neutrophils after dietary supplementation with eicosapentaenoic acid. Proc Natl Acad Sci U S A 1985;82:1540–4.
[19] Fredman G, Serhan CN. Specialized proresolving mediator targets for RvE1 and RvD1 in peripheral blood and mechanisms of resolution. Biochem J 2011;437:85–97.
[20] Spite M, Norling LV, Summers L, Yang R, Cooper D, Petasis NA, et al. Resolvin D2 is a potent regulator of leukocytes and controls microbial sepsis. Nature 2009;461:1287–91.
[21] Hasturk H, Kantarci A, Gougout-Surmenian E, Blackwood A, Andy C, Serhan CN, et al. Resolvin E1 regulates inflammation at the cellular and tissue level and restores tissue homeostasis in vivo. J Immunol 2017:179:7021–9.
[22] Titoes R, Rius B, González-Pérez A, López-Vicario C, Morán-Salvador E, Martínez-Clemente M, et al. Resolvin D1 and its precursor docosahexaenoic acid promote resolution of adipose tissue inflammation by eliciting macro- phage polarization toward an M2-like phenotype. J Immunol 2011;187: 5408–18.
[23] Serhan CN, Yang R, Martinez K, Kasuga K, Pillai S, Porter TF, et al. Maresins: novel macrophage mediators with potent antiinflammatory and proresolving actions. J Exp Med 2009;206:1591–604.
[24] Dalli J, Ramon S, Norris PC, Colas RA, Serhan CN. Novel proresolving and tissue-regenerative resolvin and protectin sulfido-conjugated pathways. FASEB J 2015;29:2120–36.
[25] Dalli J, Zhu M, Vlasenko NA, Deng B, Haeggstrom JZ, Petasis NA, Serhan CN. The novel 13S,14S-epoxy-maresin is converted by human macrophages to maresin 1 (MaR1), inhibits leukotriene A4 hydrolase (LTA4H), and shifts macrophage phenotype. FASEB J 2013;27:2573–83.
[26] Murthy S, Gomella CD, Fowler RA. Care for critically ill patients with COVID-19: what clinicians need to know. Nutr Clin Pract 2009;24:487–99.
[27] Glende J, Schwegmann-Wessels C, Al-Falah M, Pfefferle S, Qu X, Deng H, et al. Importance of cholesterol-rich membrane microdomains in the interaction of the S protein of SARS-coronavirus with the cellular receptor angiotensin-con- verting enzyme 2. Virology 2008;381:215–21.
[28] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020:395:1044–62.
[29] Langlois PL, D’Aragon F, Hardy G, Manzanares W. Omega-3 polyunsaturated fatty acids in critically ill patients with acute respiratory distress syndrome: a systematic review and meta-analysis. Nutrition 2019:61:84–92.
[30] Padelli I, Mayer K, Klek S, Omar Alsaleh AJ, Clark RAC, Rosenthal MD, et al. ω-3 fatty-acid enriched parenteral nutrition in hospitalized patients: systematic review with meta-analysis and trial sequential analysis. JPN J Parenter Enteral Nutr 2020;44:44–57.
[31] Murthy S, Gomella CD, Fowler RA. Care for critically ill patients with COVID-19 [E-pub ahead of print]. JAMA 2020.
[32] Feehan KT, Gilroy DW. Is resolution the end of inflammation? Trends Mol Med 2019;25:198–214.
[33] Rius B, La Meij Bejs, van Bolhork-de van der Schuven MA, Langius JA, Brouwer IA, van Leuwen PA. n-3 PUFAs in cancer, surgery, and critical care: a systematic review on clinical effects, incorporation, and washout of oral or enteral compared with parenteral supplementation. Am J Clin Nutr 2011;94:1248–55.
[34] Hall TC, Bilku DK, Neal CP, Cooke J, Fisk HL, Calder PC, Dennison AR. The impact of an omega-3 fatty acid rich lipid emulsion on fatty acid profiles in critically ill septic patients. Prostaglandins Leukot Essent Fatty Acids 2016;112:1–11.
[35] Bariro KV, Cassulo AP, Schalch L, Munhoz ED, Manetta JA, Calder PC, Silveira VL. Pharmacoinmunition: acute fatty acid modulation of circulating cytokines in elderly patients in the ICU. JPN J Parenteral Enteral Nutr 2014:38:467–74.
[36] de Miranda Torrinhas RS, Santana R, Garcia T, Cury-Boaventura MF, Sales MM, Curi R, et al. Parenteral fish oil as a pharmacological agent to modulate postoperative immune response: a randomized, double-blind, and controlled clin- ical trial in patients with gastrointestinal cancer. Clin Nutr 2013;32:503–10.
[37] Sungurtekin H, Değirmenci S, Sungurtekin U, Oguz BE, Sabir N, Kaptanoğlu B. Comparison of the effects of different intravenous fat emulsions in patients with systemic inflammatory response syndrome and sepsis. Nutr Clin Pract 2011;26:665–71.

[38] Hall TC, Bilku DK, Al-Leswas D, Neal CP, Horst C, Cooke J, Metcalfe MS, Dennison AR. A randomized controlled trial investigating the effects of parenteral fish oil on survival outcomes in critically ill patients with sepsis: a pilot study. JPEN J Parenter Enteral Nutr 2015;39:301–12.

[39] Barros KV, Cassulino AP, Schalch L, Della Valle Munhoz E, Manetta JA, Noakes PS, Miles SA, et al. Supplemental intravenous n-3 fatty acids and n-3 fatty acid status and outcome in critically ill elderly patients in the ICU receiving enteral nutrition. Clin Nutr 2013;32:599–605.