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Proposing Vascepa (Icosapent Ethyl) as Supplemental Treatment Targeting the Underlying Causes of Persistent, Post-Viral Symptoms Associated with COVID-19: A Case Series

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ABSTRACT

Current treatment options of post-viral COVID-19 symptoms lack conclusive evidence of success in infected individuals, leaving a desperate need for alternative treatments. In this study, we propose the use of icosapent ethyl (IPE), a pure esterized form of omega-3 fatty acid eicosapentaenoic acid (EPA), for its current use as a cell membrane stabilizer, anti-inflammatory and antithrombotic agent. This case series consists of patients, all of which experienced persistent post-viral symptoms of COVID-19 weeks to months after incidence of infection. Each patient reported considerable improvement of various COVID-19 symptoms including post-exertional malaise, cognitive impairment, and dermatologic complaints, primarily hair loss and onycholysis. As a result, we believe each of these individual outcomes collectively provide a starting point in demonstrating the potential success of IPE in treating persistent COVID-19 symptoms brought on by systemic hyperinflammation and hypercoagulation. In doing so, we hope to spark additional research detailing clinical outcomes of IPE administration to treat COVID-19.

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Introduction

The COVID-19 pandemic caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has resulted in millions of deaths worldwide [1]. First evidence of SARS-Cov-2 localized its origin to a live seafood market in Wuhan, China, indicating the likelihood of zoonotic transmission. However, as incidence of SARS-Cov-2 in humans rapidly escalated, it became evident this was in conjunction with person-to-person transmission [2]. Additionally, the increase in affected individuals drew attention to the widespread clinical spectrum caused by infection, ranging from an asymptomatic presentation or mild upper respiratory tract illness to severe viral pneumonia with respiratory failure or possibly death [3]. Airborne transmission of SARS-CoV-2 by means of respiratory droplets most commonly presents with respiratory illness and an exaggerated inflammatory response, often leading to adult respiratory distress syndrome (ARDS) [2,3]. Limitations placed on data collection detailing additional clinical manifestations of COVID-19 include social distancing, isolation, as well as reluctance to seek treatment. These factors not only serve as an obstacle for understanding this novel virus but effectively contribute to poorer clinical outcomes of the infection due to delay of medical intervention [4].

The numerous and widely varying aspects of systemic COVID-19 disease are slowly being uncovered as time into the pandemic continues. Most notably, neurological manifestations and cerebrovascular disease. Interestingly, evidence of this has shown life-threatening neurological conditions, such as an ischemic stroke, can occur in previously asymptomatic individuals. According to a retrospective study regarding cerebrovascular

disease as a complication of COVID-19, the incidence of stroke presentation among hospitalized patients was approximately 5% [5]. Neurological manifestations, including strokes, are thought to result from multiple viral-induced mechanisms including hyperinflammatory and hypercoagulable states, direct infection of CNS and post-infectious immune mediated processes [4-6]. Further inflammation of endothelial cells following direct infection results in subsequent vasoconstriction of blood vessels supplying the tissue. The serious implications of endothelial inflammation have been demonstrated histologically in post-mortem studies [7].

The current treatment options aimed towards hyperinflammatory states elicited by COVID-19 are scarce. Moreover, without treatment of acute hyperinflammation, the long-term complications of chronic hyperinflammation have become increasingly prevalent as data for the novel virus becomes available [8]. In a meta-analysis conducted by Taquet and co-authors, 57% of patients who tested positive for COVID-19 sought treatment for one or more core features of Post-Acute Sequelae of SARS CoV-2 (PASC), which includes dyspnea, post-exertional malaise, myalgias, parosmia, cognitive changes, headaches, chest or throat pain, anxiety or depression [8]. Furthermore, results showed significant differences in frequency of post-infection symptoms when compared to Influenza. Davis provides a more comprehensive analysis of symptoms in post-COVID-19 patients using multiple methods, which indicated a total of 203 symptoms over 10 body systems that follow consistent patterns of onset and recurrence [9]. The extent and prevalence of long-COVID symptoms highlight the novelty of the virus, as well as the increasing necessity of treatment options.

This case series aims to minimize this gap by proposing a supplemental treatment of COVID-19 specifically targeting postviral hyperinflammatory states brought on by the infection, as well as complications secondary to infection. To achieve this, we utilize the ethyl ester of omega-3 fatty acid eicosapentaenoic acid (EPA) known as icosapent ethyl (IPE). The use of IPE was mainly due to its role in the treatment of persistent hyperglyceridemia, supported by research findings denoting its influence on anti-inflammatory activity and reduction of cardiovascular risk [10-13]. In addition to studies, clinical trials have demonstrated a positive correlation between IPE and EPA treatment and the reduction of inflammatory markers [12-15]. Other potentially beneficial effects that have been attributed to IPE include antioxidant effects, arterial plaque modification and regression, antithrombotic and antiplatelet effects, endothelial cell membrane stabilization, and enhanced endothelial function [12].

However, studies administering EPA from alternative sources revealed inconsistencies in its effect with respect to the relative purity of EPA. This finding prompted an analysis of serum EPA when administered alone and with other omega-3 fatty acids, primarily DHA and AA. Results showed there was a statistically significant improvement when given pure EPA versus six impure EPA samples [16]. Additionally, further evidence supports this hypothesis when using generic EPA and branded pure EPADEL [17]. Therefore, with sufficient clinical evidence to suggest on-label use of EPA is affected by its purity, we believe off-label use in long-term COVID-19 patients follows the same trend. In this study, we report the application of IPE in the treatment of post-viral sequelae common of long-COVID infections with an additional consideration for EPA purity in Case 1.

Case Series Presentation

Case 1

A 55-year-old Caucasian woman with an unremarkable past medical history was infected with Sars-Cov-2 in April 2020. She appeared to be an asymptomatic carrier until she developed a stroke requiring tissue plasminogen activator (tPA), a strong clot dissolving medicine. Her computed tomography (CT) scan and CT angiogram showed an infarction of the right middle cerebral artery. Her symptoms included: reduced level of consciousness, dysphasia, hemiplegia on left side, dysarthria, sensory deficit, and dysgeusia, a distortion in the sense of taste. The patient was started on aspirin 325 mg daily as well as a high-intensity statin. Neurologic symptoms gradually began to improve over the ensuing days. After three months many symptoms improved, but she continued experiencing long-COVID symptoms including dysgeusia, post-exertional malaise, insomnia, and brain fog. At this time, it was found the patient had been supplementing with fish oil prior to her infection, which contains both EPA and DHA. In an effort to optimize EPA purity and lower DHA intake, she was started on oral Vascepa at 4 grams per day. After three days on this dose, she reported more lucid thinking, improved mood and sleep, as well as overall increased energy. After two weeks on this dose, her cognitive function and post-exertional malaise returned to her baseline before infection. Unfortunately, some residual stroke symptoms persisted, including unilateral numbness.

Case 2

The next case in this series is a 32-year-old Caucasian man with no prior medical history who became infected with Sars-Cov-2, which was verified by PCR on January 29th, 2021. After 2 months post diagnosis, he reported a chronic cough and brain fog two months after being diagnosed, at which point he began 4 grams per day of Vascepa. In a matter of 3 days, his brain fog began to improve, which was followed by improvement of his chronic cough after just 2 weeks. He changed the dosage to 2 grams per day after this and at 1 month, his cough completely resolved.

Case 3

Case 3 involves a 49-year-old African American woman without a prior medical history. She tested positive for COVID-19 in August of 2020 and was unvaccinated at the time of infection. After 6 days of hospitalization with low oxygen saturation, she was diagnosed with post-COVID pneumonia. Following her initial infection, she continued experiencing long-COVID symptoms in January of 2021 including parosmia, hair loss, and recurrent onycholysis affecting multiple toenails. At this time, she started Vascepa 4 g daily for two weeks then remained on 2g daily for 3 months. Since her initial IPE dose started during the second toenail regrowth period, she showed marked improvement of nail regrowth and no further onycholysis. Additionally, hair loss subsided two weeks after starting IPE and hair regrowth began after one month. Within two months on IPE 2 g daily, her hair returned to normal appearance.

Case 4

Case 4 is a 37 year old Caucasian woman who presents with PASC after testing positive in the spring of 2020. Her primary care physician diagnosed her with postural orthostatic tachycardia syndrome (POTS), mast cell activation syndrome (MCAS), and chronic fatigue syndrome during her year-long progressive decline. She then experienced some relief with symptomatic treatments including Ketotifen and low-dose Naltrexone (LDN) along with daily multivitamins and Lovaza 2 g daily. At the time of treatment, she had been vaccinated and boosted with mRNA vaccine. She was on physical disability and noted brain fog, parosmia and phantosmia, and post-exertional malaise in which walking was limited to no more than ¼ miles and around 50% of her day was spent laying down. She was taken off Lovaza and started Vascepa

4 grams daily. She noticed significant improvement after two weeks. During 2 week follow-up, she reported walking 1 mile and higher tolerance to exercise and reduced brain fog. She denied any parosmia or phantom smells. At this time, she lowered the dose to Vascepa 2 grams daily. Prior to Vascepa, her symptoms were best controlled by LDN and Ketotifen, though she reported a higher degree of improvement with Vascepa.

Case 5

The final case involves a 66-year-old Caucasian woman with an unremarkable medical history presenting with a covid-19 post vaccine injury. She had a second mrna dose in Winter 2021. She developed hip and knee pain as well as hair loss. She treated these symptoms unsuccessfully with prednisone. She started Vascepa at 4 grams daily for two weeks then tapered the dose to 2 grams daily for two more weeks. After a week she noticed that her hair stopped falling out and after the second week her joint pain mostly resolved. By the end of the month she was symptom-free.

Discussion

The first presentation in this series involved a previously healthy 55-year-old female who developed a stroke as an otherwise asymptomatic individual. After her neurological symptoms swiftly improved with standard management, the persistence of symptoms secondary to ischemic stroke and post viral COVID-19 required further treatment. Within the days following induction of IPE treatment, she reported rapid improvement of post-exertional malaise, difficulty sleeping, and problem solving ability. This finding was further supported by the following patients in the case series, all of which denoted signs of recovery to baseline shortly after beginning IPE treatment. The astounding return to baseline preceding infection demonstrates the utility of IPE in acute inflammatory states, specifically regarding COVID-19 infections.

Evidence suggests stroke onset of the 55-year-old female stroke patient was most likely a consequence of the hypercoagulable and hyperinflammatory states resulting from the presence of SARS-CoV-2, both of which are targeted by IPE. These findings align with previous clinical trials regarding the anti-inflammatory effect of IPE [18] by means of reducing circulatory presence of inflammatory markers [10]. In addition to this immune modulation, relief of hypercoagulable states due to IPE treatment is supported by its antithrombotic and anti-platelet effects, which we believe assisted in patient's in stroke recovery. IPE as well as EPA have also demonstrated improvement in endothelial function and inhibition of replication of hepatitis C virus and influenza, both being enveloped viruses similar to SARS-CoV-2 [18,19]. The increase in lucid thinking and improved mood is supported by evidence which suggests IPE can enhance microglial function and improve certain mood disorders [20]. Furthermore, Case 1 also demonstrated the necessity of pure EPA for optimal function, as her long-COVID symptoms persisted with EPA and DHA mixture.

In order to fully understand the mechanism of action facilitated by IPE, additional research into the molecular basis of the drug is needed. Furthermore, indisputable evidence regarding clinical applications of IPE for treatment of a variety of conditions, including COVID-19, requires more comprehensive studies using larger sample groups.

Conclusion

Through this case series we report the first evidence of IPE as treatment for post-viral symptoms secondary to SARS-CoV-2 infection and propose an explanation for inconsistencies in clinical improvement with generic, impure EPA.While the current mechanism by which EPA uptake is affected by contaminant omega-3 fatty acids is unknown, we suggest preferential binding for DHA with respect to EPA. Due to the anecdotal nature of this study, we emphasize the need for larger scale research using a more representative sample population in order to unequivocally confirm the clinical efficacy of IPE. Through this study, we hope to spark much needed research directed towards long-COVID clinical manifestations.

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