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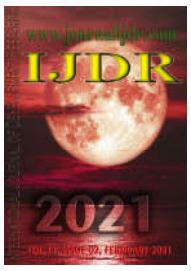

RESEARCH ARTICLE OPEN ACCESS

SEVERE ACUTE RESPIRATORY SYNDROME: PROPOSED NEW EVIDENCE-BASED TREATMENT FOR SARS-COV-2

***[1]Júlio Fernandes LEITE, [2]Umberto EUZEBIO**

[1]Associação dos Servidores da Fundação Universidade de Brasília – ASFUB – Campus Universitário Darcy Ribeiro, CEP 70910-900 – Brasília – DF, Brasil. [2]Centro de Estudos Avançados e Multidisciplinares da Universidade de Brasília – CEAM/UnB– Campus Universitário Darcy Ribeiro CEP 70910-900 – Brasília – DF, Brasil

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****Corresponding author: Umberto Euzebio,***

ABSTRACT

The new coronavirus (SARS-CoV-2) pandemic is a worldwide challenge due to the urgent need to develop a treatment that reduces mortality from COVID-19 (new coronavirus disease). As there are still no drugs to combat SARS-CoV-2, the objective of this work was to search scientific information about SARS-CoV-2 and COVID-19 pathogenesis in order to propose a new evidence-based therapy. As a methodology, we use keywords released in the Medline index databases with crossing information. In the text we present the complex pathogenesis of COVID-19, with multiple factors that lead to severe lung injuries and the spread of the virus to other organs. Preliminary results from case studies and animal models of the disease suggest that there are two interconnected inflammatory pathways that must be inhibited simultaneously to interrupt the marked inflammatory process that occurs in severe cases: toll-like receptors and CCR5. With the analysis of the information obtained, we tried to find alternatives for possible interventions for simultaneous inhibition of the two main pro-inflammatory pathways probably involved in SARS-CoV-2.

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INTRODUCTION

The global crisis faced by the new coronavirus (SARS-CoV-2) pandemic caused a series of challenges and innovations across society, leading us to reflect on the impact of our behaviors on the economy, society and health. The severe acute respiratory syndrome caused by SARS-CoV-2 is characterized by symptoms such as fever, cough, and progressive dyspnea, respiratory failure, in addition to other possible symptoms, such as anosmia and loss of taste, clotting disorders, among others, and constitutes the new coronavirus disease, COVID-19. With the pandemic in Brazil starting in 2020, COVID-19 became one of the main causes of death, surpassing 210 thousand deaths in February 2021. The lack of information, the spread of fake news and the mismatched guidelines by public authorities have contributed even more to the spread of the virus among the population. One way to expand the sources of information may be the open access scientific papers. Important information for public health and its dissemination in the press is essential when presenting news to the public that can affect their lives in a beneficial or harmful way. Keeping a population informed about such events benefits them, so that the citizen can be informed about scientific information and, with this knowledge, is able to actively exercise their citizenship in society. (Melo *et al*., 2020).

Great efforts have been made to disseminate scientific information in response to the demands of society in times of pandemic. Research on media shows that which sectors that are dedicated to public communication can and should be considered one of the most expressive and most evident features of the process of expanding communicational practices in science communication whether they are journalists / disseminators of science or sources / scientists, in direct or indirect contact with the public, especially in pandemic situations, such as COVID-19 (Santos, Almeida and Crepaldi, 2020). These are attitudes that support the proposition of open science practices, enabling greater dissemination of information because, to deny the institutionalization of scientific information is to subtract from society the opportunity to qualify their opinions based on science. (Costaand Veiga, 2020). Thus, the sharing and opening of data should be encouraged, in the same way as citizen participation in research, it is necessary that the information reaches the population. Reflecting on the importance and use of scientific journals in academic and social contexts, the author states that in an "environment in which false news and discrediting by science are growing, valuing and disseminating scientific knowledge can be seen as an urgent matter.(Cardoso, 2020, p. 1). The dissemination of scientific knowledge acts directly in the fight against fake news, especially at the time of the Covid-19 pandemic, it is necessary that

the material created reaches the audience that is at home, circulating in the same vehicles as fake news, that is, via social networks and platforms on the internet, through the production of podcasts, videos, lives etc. It is important to know that the people who develop scientific dissemination content are concerned with the language used and in the production of content that is attractive to an audience that is constantly bombarded by a plethora of materials originating from different sources (Dantas and Deccache-Maia, 2020). Regarding the importance of using scientific journals in the social context, the distrust of what is developed in universities or research centers is due to the low visibility, in places outside the academic community, of what is being researched, is discussed and produced in these environments.(Cardoso, 2020). As there are still no effective drugs for the treatment of COVID-19, the media is attentive to the knowledge that is being produced by the scientific community worldwide.

MATERIAL AND METHODS

The aim of this work was to search scientific information about SARS-CoV-2 and pathogenesis of COVID-19 in order to understand the mechanisms involved in the disease and to propose a new evidence-based therapy. As methodology we initially crossed keywords SARS-CoV-2, COVID-19, pathogenesis and physiopathogenesis published in the Medline index database. Identifying the multiple factors that mediate the complex disease process, especially their relationship with the severity of the disease, we did another search in the Medline index database using as keywords the main mediators of pathogenesis in search of their inhibitors. From this set of information, we proposed a new treatment for COVID-19 based on evidence, as shown below.

RESULTS AND DISCUSSION

Characterization of Sars-CoV-2: The new coronavirus identified in 2019 (SARS-CoV-2) is causing a pandemic that has sparked a frantic search for effective strategies to combat COVID-19, a situation where the drugs currently available and widely used to treat other diseases represent a gain in terms of time, given the urgency required for the treatment of the pandemic. The pathogenesis of COVID-19 is complex, with multiple factors leading to severe lung damage and spread of the virus to other organs: high viral load, systemic infection, a cytokine storm, massive pulmonary infiltration by monocytes and macrophages, bronchiolitis, interstitial pneumonitis, diffuse alveolar damage and fibrotic healing. The pathogenesis of COVID-19 in patients begins with the binding of SARS-CoV-2 to toll-like receptors, located in different cell compartments of the plasma membrane, endoplasmic reticulum and nucleus. When activated, toll-like receptors release a cascade of pro-inflammatory cytokines, mainly IL-1 and IL-6 (Conti *et al*., 2020), by activating the transcription factor NFkB (Verzola *et al*., 2017; Benedikz *et al*., 2019). Mortality due to COVID-19 is directly proportional to the concentration of IL-6 in the blood of patients (Cai *et al*, 2020). In inflamed tissues, there is a significant increase in oxidative stress, which also activates toll-like receptors, which contributes to tissue damage in inflammatory lung diseases (Yanagisawa *et al*., 2009). For a review of the toll-like receptor system in the innate immune response see other sources (Javaid, Yasmeen and Choi, 2019; Anwar *et al*., 2019).

Biochemical and Physiological Interactions: The CCR5 protein is a member of the CC chemokine receptor family that is expressed in several hematopoietic cells, including lymphocytes and macrophages, in addition to epithelial and endothelial cells. Chemokines capable of binding to CCR5 include CCL3 (MIP-1a), CCL4 (MIP-1b) and CCL5 (RANTES). CCR5 gained attention when it was discovered that it is a necessary co-receptor for the entry of HIV into leukocytes (Deng *et al*., 1996). Later, according to research results, it was found that CCR5 is an important molecule in the regulation of the immune response, as well as in the attraction of macrophages and in the activation of T lymphocytes at the site of inflammation and infection. Blocking CCR5 with antagonists is increasingly being proposed as a strategy to combat inflammatory diseases and infections in which this receptor plays an important role (Vangeslista and Vento, 2018). Severe acute coronavirus respiratory syndrome in mice 12 to 14 months of age is an experimental model of disease that simulates the characteristics of COVID-19 in humans (Chen *et al*, 2010). In this model, after intranasal administration, the coronavirus replicates in the lungs, with a maximum peak in 2 days, accompanied by increased production of cytokines (TNF-α, IL-6, CXCL10, CCL2, in addition to CCL3 and CCL5, with the last two bind and activate CCR5) and the migration of leukocytes (NK cells and macrophages) to the lungs. On the seventh day, there is histological evidence of pneumonitis and a decrease in the viral population, but in that period there is a second wave of increased cytokine production (TNF-α, IL-6, interferon gamma, IL-2, IL-5, CXCL9, CXCL10, CCL2, CCL3, CCL5 and CXCR3, CCR2 and CCR5 receptors) and T lymphocyte infiltration (Chen *et al*, 2010). The elevation of CCL5 in the blood of patients is associated with the severity of the clinical picture of COVID-19 (Peterson *et al*., 2020), suggesting that CCR5 inhibition has potential in the treatment of COVID-19, by inhibiting the excessive inflammatory response (Chua *et al*., 2020). In COVID-19 there is a high occurrence of thrombotic complications, with the formation of fibrin plugs and platelets in the pulmonary arterioles, which contributes to respiratory failure and risk of death. It is already established that the activation of inflammation, through activation of NFkB and toll-like receptors, is involved in this process (Dinicolantonio and Mccarty, 2020).

Inflammation is known to play an important role in the risk of cardiovascular disease, and the expression of various cytokines and their receptors, including CCR5, is related to the risk of developing cardiovascular disease (Martynowicz, *et al*., 2014). Diabetes patients are at increased risk of cardiovascular events, and there is an increase in CCR5 and NFkB in the blood leukocytes of patients with type 2 diabetes, but especially when they are not in adequate glycemic control (Inayat, Azim, Baloch, 2019). Therefore, the increase in CCR5 and NFkB that occurs in diabetic individuals may predispose these patients to a more pronounced inflammatory reaction in the development of COVID-19. In patients with COVID-19, the serum concentration of IL-6 is directly related to the risk of fatal outcome and is higher in diabetics (Cai *et al*, 2020). There is evidence that PPAR-γ agonists, such as pioglitazone, can inhibit the inflammatory response triggered by activation of toll-like receptors (Dana, Vaseghi andJavanmard, 2019). If modifying the treatment of diabetic patients with COVID-19 to include pioglitazone can decrease pulmonary inflammation in patients, it is still an unexamined hypothesis, but a study (Kaplan *et al*, 2018) in patients with sepsis admitted to a In intensive care, the use of pioglitazone (0.5 mg / kg / day) significantly decreased the serum concentration of IL-6. Studies have shown that free fatty acids, such as palmitate, by activating a toll-like receptor induce the expression of CCL3 (MIP-1a) (Ahmad *et al*, 2019), one of the activators of CCR5, and the concentration of CCL3 in the circulation it is increased in people with metabolic syndrome (a set of factors that increase the risk of cardiovascular disease, such as elevated blood pressure, glucose, obesity, increased blood fats and insulin resistance). These facts have three important consequences: (1) the activation of the inflammatory response through the toll-like receptors is also capable of activating the inflammatory pathway that involves CCR5, since CCL3 is a ligand and activator of CCR5; (2) the two inflammatory pathways, one involving toll-like receptors and the other activated by CCR5, must be inhibited simultaneously in order to have more success in controlling the inflammatory response in COVID-19; (3) patients with metabolic syndrome may also be at an increased risk of developing more severe inflammation in COVID-19. COVID-19 has a much higher mortality rate in men than in women (Mo *et al*, 2020). Likewise, it is also found that most men are at higher risk of cardiovascular disease than women and, on the other hand, cardiovascular diseases are a risk factor for death from COVID-19. Thus, this could be an explanation for the higher mortality due to COVID-19 in men than in women, but a hormonal factor should not be ruled out.

There is evidence that sex hormones affect the immune system and men are known to be at lower risk for autoimmune inflammatory diseases, such as Sjogren's syndrome, systemic lupus erythematosus (SLE), autoimmune thyroid disease, scleroderma, rheumatoid arthritis (RA) and multiple sclerosis (Ortona *et al*, 2020). In some of these diseases, such as SLE and RA, men are affected at an older age than women (Ortona *et al*, 2020). These findings are in accordance with the serum testosterone concentration, which reaches its peak in the third decade of life and subsequently decreases by up to 2% per year, so that there is a greater proportion of elderly men with lower testosterone concentrations. (Mcbride, Carson, Coward, 2016), or total testosterone concentration <350 ng / dL. We emphasize that reporting the possible direct effects of testosterone on the immune system is beyond the scope of this paper, but one must be highlighted in particular. In a study on intraprostatic dihydrotestosterone (Fan *et al*, 2014) they state that there is evidence that the activation of androgen receptors inhibits the expression of CCR5. Advanced age may be the main unmodifiable risk factor for the development of COVID-19, but the increased expression of CCR5 in men with low testosterone (more frequent in obese, alcohol abusers, who had mumps, chemical or surgical castration prostate or testicular cancer), regardless of age, may be linked to a higher incidence of fatal outcome of this disease in men. On the other hand, studies have shown that estrogenic activity, like medroxyprogesterone, increases the expression of CCR5 in leukocytes (Mo *et al*., 2005; Maritz *et al*., 2018). Thus, in elderly women, due to menopause, there would be no increase in the expression of CCR5, which could contribute to lower mortality from COVID-19 in elderly women than in elderly men. Thus, based on clinical studies in patients with COVID-19 and an experimental model of the disease in animals, it appears that two inflammation activation pathways should be simultaneously inhibited to more successfully reduce the exacerbated lung inflammation of the disease: toll-like receptors and via CCR5. Glucocorticoids and non-steroidal anti-inflammatory drugs are not able to inhibit CCR5 or toll-like receptors, on the contrary, they can even increase the expression of these proteins (Elovaara *et al*., 2006; Ji *et al*., 2016; He *et al*, 2019). Thus, theoretically they could contribute to the worsening of the inflammatory reactions generated by the coronavirus. The identification of the protein that serves as the gateway to SARS-CoV-2 in cells may be less important from the point of view of strategies to fight infection at the current moment of the pandemic. This is because several cell surface proteins have been identified that can perform this function, and it can be difficult to know which one is really important (Qi *et al*., 2020).

Pharmacotherapy: Drugs available for the treatment of other diseases and capable of inhibiting viral proliferation have been suggested for the treatment of COVID-19. The low-cost commercially available hydroxychloroquine antimalarial, contraindicated for children under 6 years of age, has relatively low toxicity (the risk of side effects such as retinopathy and cardiomyopathy in patients with COVID-19 is still unknown). This drug inhibits CCR5, inhibits the binding of various viruses to the cell surface, has been shown, in vitro, to be effective in inhibiting several types of RNA and DNA viruses, including coronavirus, rabies virus, poliovirus, hepatitis A, B and C viruses, herpesvirus, influenza A and B viruses, Zika, dengue and Chikungunya viruses, among others. Regarding hydroxychloriquine, it was found that it inhibits the MAPK pathway (which many viruses use to activate their intracellular replication) and has an anti-inflammatory effect (inhibits IL-1, IL-6 and TNF-alpha). A preliminary study with hydroxychloroquine in patients with COVID-19 suggested a positive result, but there is still no unequivocal proof of the drug's effectiveness (Devaux, 2020). Another potential drug would be maraviroc, a competitive CCR5 inhibitor, approved for clinical use as an inhibitor of the entry of HIV-1 into leukocytes (Woollard, Kanmogne, 2015). Although the drug repurposing of maraviroc was suggested, there are still no published studies on its effect on COVID-19, and there is no evidence that maraviroc has the capacity to inhibit toll-like receptors. Nitazoxanide is a low-cost antiparasitic, has low toxicity and is approved for children over 1 year (7.5mg or 0.375ml / kg twice a day, for up to 14 days). This drug inhibits the expression of CCR5, has a broad spectrum antiviral effect, inhibiting the in vitro replication of RNA- and DNA-viruses, including respiratory syncytial virus, and inhibits the proliferation of influenza viruses resistant to neuraminidase-inhibiting drugs, which makes it a high-value drug in situations of coronavirus co-infection with the influenza virus. Nitazoxanide also acts to inhibit parainfluenza, coronavirus, rotavirus, norovirus, hepatitis B, hepatitis C, dengue, yellow fever, Japanese encephalitis virus and HIV viruses, in addition to inhibiting HIV replication by 87% (demonstrating a high capacity to inhibit the expression of CCR5) (Trabattoni *et al*., 2016). Nitazoxanide improves symptoms and reduces the duration of infections by the influenza virus at a dose of 600 mg twice daily for 6 consecutive days (Rossignol, 2014) and has high antiviral activity against the coronavirus in vitro (Cao, Forrest, Zhang, 2015). Pharmacokinetic studies suggest that higher than usual but clinically safe doses of nitazoxanide would be able to produce concentrations with an effective antiviral effect in vivo, and although its use has been proposed in patients with COVID-19 (Rajoli *et al*., 2020), there are still no published results. The herbal medicine Pinus pinaster extract, patented name Pycnogenol, is used with great success in the treatment of edematous and inflammatory conditions, such as edema of venous insufficiency (Belcaro *et al*., 2017), osteoarthritis at a dose of 200mg per day (Jessberger *et al*., 2017) and Sjogren's syndrome (Luzzi *et al*., 2018). In addition, pycnogenol has beneficial effects in animal models of pulmonary fibrosis in COPD (Ko *et al*., 2017), asthma (Shin *et al*., 2013) and lung injury induced by mechanical ventilation (Xia *et al*, 2015). Pycnogenol contains polyphenolic antioxidant substances (catechins, caffeic acid, ferulic acid and taxifoline), with anti-inflammatory effect, which are quickly absorbed. The active metabolites, produced by the intestinal microbiota in the intestinal tract from oligomeric procyanidins (catechin oligomers), appear in the blood 6 hours after ingestion and remain for at least 14 hours, have wide tissue distribution, can be detected in the blood cells, providing a lasting flow of anti-inflammatory substances (Rohdewald, 2018). The anti-inflammatory mechanism of pycnogenolinvolves: inhibition of the transcription factor NFkB; inhibition of toll-like receptors (Verlaet *et al*., 2019); decreased serum concentration of IL-1 (Shin *et al*., 2013; Xia *et al*, 2015; Belcaro *et al*., 2017), IL-6 (Shin *et al*., 2013; Xia *et al*, 2015; Verlaet *et al*, 2019) and TNF-alpha (Peng, Wei, Lau, 2000; Xia *et al*, 2015; Verlaet *et al*, 2019). We did not find in our survey reports on the effect of pycnogenol on CCR5 inhibition.

The antibiotic azithromycin has the ability to inhibit toll-like receptors, has some anti-inflammatory effect and in vitro studies show a synergistic effect with pentoxifylline in decreasing the production of IL-1, IL-6 and TNF-alpha (Speer *et al* ., 2018). In our search we found no articles showing inhibition of NFkB, CCR5 or benefits in viral infections, which is in agreement with (Mazzitelli *et al*. 2020) who still claim that there is no unequivocal evidence of benefits from the use of azithromycin associated with hydroxychloroquine in geriatric patients with COVID-19. Simvastatin is a low-cost, safe drug, widely used in the treatment of hypercholesterolemia, which effectively reduces the risk of cardiovascular events (Collins *et al*., 2016), and has several other effects not related to cholesterol reduction, such as lowering cholesterol inflammatory response. Several experimental studies indicate that the anti-inflammatory effect of simvastatin is mediated by inhibition of the transcription factor NFkB, with a decrease in the activity of IL-1, IL-6 and TNF-alpha (Mcfarland, Davey, Anoopkumar-Dukie, 2017; Boland *et al*., 2018; Qin *et al*., 2019). But simvastatin also significantly reduces levels of MCP-1 (monocyte-1 chemo-attracting protein), CCL5, regulates the expression of the chemokine receptors CCR2 and CCR5 (Yin *et al*., 2007) and inhibits the expression of toll-like receptors in leukocytes of patients with hypercholesterolemia (Moutzour *et al*., 2012). A randomized, double-blind, placebo-controlled pilot study of simvastatin 80 mg or placebo for 7 days in patients aged 55 and over and community-acquired pneumonia with sepsis admitted to a secondary care hospital was associated with better scores in the Sequential Assessment of Organ Failures compared to placebo. A post hoc analysis showed that simvastatin therapy was associated with better hospital-free survival compared to placebo. Simvastatin was well tolerated in this group of elderly and multimorbid patients with co-prescription of antibiotics (Sapey *et al*., 2019).

The use of simvastatin or atorvastatin, but not rosuvastatin, for> 30 days before admission to sepsis, was associated with improved survival in 30 days, which shows that the beneficial effect of statins does not depend on its potency (Lee *et al* ., 2018). There are no published studies on the use of simvastatin in the treatment of COVID-19 patients. Quercetin is a polyphenolic substance found mainly in onion and yerba mate, Ilex paraguariensis, which has an anti-inflammatory effect through the inhibition of toll-like receptors, of CCR5 expression, and NFkB, with decreased secretion of IL-1, IL-6, TNF-α, in leukocytes (Noh *et al*, 2014; Bhaskar, Helen, 2016), by a mechanism that involves increased PPAR-γ activity (Zhang *et al*., 2016; Xiong *et al*., 2019). Quercetin also has antiviral effects against herpes simplex virus type 1 by inhibiting toll-like receptors (Lee *et al*., 2017), against SARS-CoV (Nguyen *et al*., 2012), and inhibits macrophage toll-like receptors alveolar (Yasui *et al*., 2015), which suggests a potential effect in the treatment of pulmonary viral inflammations. In addition, studies studies have shown (Hohmannn *et al*., 2019) that quercetin inhibits pulmonary fibrosis in animals. In a study on quercetin supplementation in patients with chronic obstructive pulmonary disease (COPD) it was shown that the dose of 2,000mg / day of quercetin is well tolerated for up to 1 week.

Conclusion

Given the above and from the analysis and discussion of the articles we can propose that simultaneously inhibition of the two main pro-inflammatory pathways probably involved in COVID-19, with low-cost, low toxicity and widely used drugs, which act through multiple mechanisms of action, increases the chance of synergism between the compounds used. Thus, we suggest the evaluation, in 7-day protocols, of the association of three products, not yet tested:

1. Pycnogenol (200 mg per day; inhibitionofNFkB, antioxidantinhibitionoftoll-like receptors, inhibitionof IL-1, IL-6 and TNF-α); it shouldnotbeused in isolation as it has no effecton CCR5;
2. Simvastatin (80 mg per day; inhibitionofNFkB, toll-like receptors, IL-1, IL-6 and TNF-α, inhibitionof CCR5 and its ligand CCL5);
3. Quercetin (500mg 4 times a day; inhibitionof CCR5, toll-like receptors, NFkB, IL-1, IL-6 and TNF-α; pulmonaryanti-fibroticeffect; in vitro effectagainstothercoronaviruses).
4. In diabeticpatients, introducepioglitazone (0.5 mg / kg / day) and monitor serum lipase.

We hope that from this article on we will be able to contribute to scientific production by opening spaces for new investigations that can add to social practices to over come this moment of uncertainty.

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