Whereas COVID-19 expands around the world, several candidate molecules including different antiviral drugs are being testing or they are under clinical trials. Also, different types of vaccines are being under research or testing in animals and humans. No definitive treatment, however, exists to date. Due to the rapid expanding SARS-CoV-2 infection, the need for effective drug treatment of COVID-19 is an increasing urgent matter.

COVID-19 is the disease caused by SARS-CoV-2 virus, an RNA β-coronavirus that, as other respiratory coronavirus, infects the respiratory track via respiratory droplets, although fecal and/or oral transmission paths are not excluded. To date, there are 15 787 461 cases, 639 012 deaths, and 9 622 749 recovered, although these data increase daily. The rapid transmission of SARS-CoV-2 may depend of several factors, including the incubation period variability (from 3 to 14 days until 27 days) before the presence of symptoms, and an elevated percent of infected subjects without symptoms, who are potential transmitters of
The excessive inflammatory response during COVID-19 is the major cause of death in these patients, leading to the use of a series of immunomodulatory agents into clinical trials but also in an off-label manner. However, from a therapeutic point of view, we must choose drugs that not only blunt the NF-κB/NLRP3 inflammasome connection during infection, but also that combat the oxidative stress response causing pulmonary and systemic damage.

In this context, we want to call the attention to melatonin. Recently, a series of reviews have been published suggesting the beneficial effects of melatonin on COVID-19, and proposing different doses of melatonin to be used. There are not, however, clinical data, and very low experimental data that demonstrated the efficacy of melatonin in viral infections, and none in SARS-CoV-2 infection, that support these proposed doses. Nevertheless, let me suggest here why melatonin may be of interest in the treatment of COVID-19 and what we need to do to support it.

It is known that melatonin has significant antioxidant and anti-inflammatory properties, and these may be of application against the free radical’s generation and inflammation in COVID-19. In 1999, we showed for the first time a dose-dependent effect of melatonin to counteracted the shock septic and multi-organ dysfunction syndrome (MODS) in a model of sepsis induced by LPS administration to rats.9 The anti-septic effect of melatonin was more pronounced in aged rats, which showed major inflammatory response.10 In both cases, melatonin, at doses of 60 mg/kg bw. restored the normal metabolic status and the function of kidney and liver in septic rats with no side effects. We also showed for the first time that the mitochondria are the main intracellular targets of melatonin, which is able to maintaining their homeostasis in conditions of strong oxidative stress even in sepsis.11,12 Melatonin also restored the normal homeostasis in every organ and tissue of mice in the model of sepsis induced by CLP and significantly increased their survival,13 supporting the utility of melatonin in the treatment of septic shock.14 We also identified the action’s mechanisms and therapeutic targets of melatonin in sepsis.15 Melatonin induces RORα-dependent bmal1 expression and, in turn, BMAL1-dependent NAMPT production, promoting the synthesis of NAD + that is used by SIRT-1 to deacetylate p65, displacing it from DNA and blocking its transcriptional activity, reducing the inflammatory response. In parallel, melatonin counteracts the mitochondrial oxidative damage as a consequence of the inflammatory reaction during sepsis; it closes the MPT and prevents the release of ROS and mtDNA to the cytosol, stopping the activation of the NLRP3 inflammasome. The subsequent lack of activation of the caspase-1 impedes the maturation of pro-cytokines including pro-IL-1β, blocking the positive feedback effect of IL-1β on its membrane receptor and further NF-κB activation.15 Melatonin becomes in the unique anti-inflammatory molecule able to block the two main pathways of the
innate immunity, NF-κB and NLRP3 inflammasome that, with its ability to recovery the mitochondrial homeostasis, explains its outstanding anti-septic properties.\textsuperscript{11,12} The doses of melatonin used in these experiments in septic mice ranged from 90 to 120 mg/kg bw., which are equivalent to that of 60 mg/kg bw used in septic rats according to dose equivalent calculation.\textsuperscript{16} Interesting, the relationship between melatonin, clock genes, and inflammatory response was recently analyzed in septic patients, showing a relationship between the degree of the inflammatory and oxidative response, the expression of \textit{bmal1}, and the levels of melatonin.\textsuperscript{17} Because septic patients exhibit a process of chronodisruption, clock genes represent another target for melatonin in this disease. Lastly, melatonin recovers lungs from oxidative damage induced by age, protecting against acute and chronic pathologies such as emphysema and pneumonia, respectively, effects that may be applicable to reduce the local oxidative and inflammatory damage in the lungs of COVID-19 patients.\textsuperscript{18}

The trinity of COVID-19, immunity, inflammation, and intervention, was defined.\textsuperscript{7} From this point of view, and from the data here presented, it is wise for us to ask an intervention with melatonin administration in COVID-19 patients to assess its efficacy and therapeutic doses. In a recent clinical trial (EudraCT: 2008-006782-83), we showed that the intravenous administration of 60 mg/d of a patented formulation of melatonin improved septic patients, reduced their mortality to zero, and their hospital stay by 40% (manuscript in preparation). The similar inflammatory response in sepsis and COVID-19, the higher incidence of the latter in aged subjects, and the similar mortality in both groups, 20%-25% in ICU patients, together with the demonstrated efficacy of melatonin against inflammation, led us to propose a clinical trial in ICU patients with SARS-CoV-2 infection. Melatonin or placebo (the same excipients than in the melatonin solution but without melatonin) will be intravenously administered every 6 hours starting at the moment at which the patient is included in the trial, at doses that are calculated accordingly.\textsuperscript{16} The trial (EudraCT: 2020-001808-42) has been just approved by the Spanish Agency of Medicines and Medical Devices (AEMPS), allowing us to identify the doses of melatonin that can be effective in this disease. The study is a phase II, single-center, double-blind, randomized placebo-controlled trial, with the objective to address the efficacy and safety of intravenous melatonin administration in ICU patients suffering from COVID-19. Besides written informed consent from patients or family members, inclusion criteria include aged above 18 years; confirmed disease with positive PCR; acute hypoxemic respiratory failure related to COVID-19; and ICU stay less that 7 days before to randomization with Murray score at the time of randomization greater or equal at ICU admission. Exclusion criteria include participation in other COVID-19 trial; liver enzymes five times higher the normal range; glomerular filtration rate less than 30 mL/min/1.73 m\textsuperscript{2}; pregnancy; autoimmune diseases; and terminal medical illness.

**CONFLICT OF INTEREST**

DA-C and GE are co-inventors of the patents "Durable preparation of an injectable of melatonin exhibiting long-term stability" (PCT/ES2015/070236), and "Injectable composition of melatonin for the treatment of viral diseases" (PCT/ES2020/070234).

**AUTHOR CONTRIBUTION**

DA-C and GE prepared the documentation of the clinical trial; JCF, PdlO, and AMB designed the protocol of the trial; DA-C, GE, and CA-F wrote the manuscript, and all authors revised its final form.

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