

Opinion

COVID-19 Related Lung Inflammation and Oxidative Stress - a Role for Cannabidiol ?

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Opinion Article

During the recent outbreak of coronavirus SARS-CoV-2, differences in susceptibilities of subjects to the infection with the virus have been observed; not all people exposed to SARS-CoV-2 become infected and not all infected patients develop severe respiratory illness. One of the biggest but still unanswered questions is why some develop severe disease, whilst others do not. Although activation of the endocannabinoid system (ECS) as well as polymorphism of the cannabinoid receptor CB2 influence susceptibility to infections with rhinoviruses [1], the role of the ECS in COVID-19 is unknown. CB2 controls the immune response and its mutant Q63R is known to be less functional and overrepresented in several populations of patients with autoimmune disease. While it increased the risk of severe acute respiratory tract infection (ARTI) in children [2], an eventually increased risk for COVID-19 is currently unknown. Age, sex and comorbidities (or comedications) seem to play a role, including medications taken early at the beginning of symptoms. Whereas risks related to comorbidities have been repeatedly described, assessments of comedications as potential risk factors are still very rare. About 60% of the subjects remain more or less asymptomatic but are carriers who can easily transmit the virus [3]. This percentage varies widely between less than 40% and up to 80% [4,5]; it reflects the lack of reliable data on asymptomatic carriers on one hand, and differences in populations concerning their sensitivity of getting diseased on the other. A minority of subjects develops apparent clinical symptoms after a mean, although variable, incubation period of about one to two weeks. A two-phase division of this clinical symptomatic stage is very important as it will influence the management of patients. The first clinical phase of roughly one week's duration can be described as a non-severe, immune defence-based, protective phase during which the development of antibodies against the virus particles is of vital importance. This phase is characterised by fever and cough as the two main symptoms, and signs of pneumonia on both lungs. During this period, measures should try to reduce virus load and to boost immune responses or at least avoid drugs that may have a negative impact. Although respective epidemiological data are still missing

for SARS-CoV-2, canonical antipyretics and antiinflammatory drugs such as paracetamol (acetaminophen) or aspirin, most of which are available without prescription and taken by patients as self medication (often as first line treatment for viral infections) must be seen with caution. A clinical benefit of these drugs for COVID-19 patients has not been demonstrated. On the contrary, preclinical studies point to an increased risk of mortality in influenza-infected animals, likely reflecting an impaired development of protective immunity [6,7,8]. In humans infected with influenza and rhinovirus, an increased duration of sickness and viral shedding, or at least no clinical benefit has been observed after intake of aspirin and paracetamol but also after a number of other medications such as COX-2 inhibitors [9,10]. Increased risks of complications of community-acquired pneumonia following prior use of non-steroidal antiinflammatory drugs (NSAIDs) have been reported also in numerous recent retrospective studies [11,12,13,14]. In addition, anticoagulants, benzodiazepines and statins which are more frequently used by an elderly population, have also been reported to reduce the virus-specific antibody response [15]. Whether ACE-inhibitors increase the risk for severe COVID-19 or not is still an ongoing debate [16,17]. Intriguingly, some patients treated for mild COVID-19 infection still had coronavirus for up to one week after symptoms disappeared, although this may be much longer in rare cases [18]. Currently, an increasing range of products with widely differing properties and mechanisms are used as experimental treatments to combat SARS-CoV-2, e.g., neuraminidase inhibitors, protease inhibitors (e.g., ritonavir, lopinavir), nucleoside inhibitors (e.g., ribavirin), inhibitors of virus replication (remdesivir), anti-sera, pegylated IFN α or (hydroxy-)chloroquine [19].

A small percentage of patients eventually progress to the second, inflammation-driven, damaging phase with a sudden deterioration around one to two weeks after symptoms onset. This phase is the most severe and characterised by an immune overreaction, with a more or less destroyed immune system, marked lymphocytopenia and an excessive, uncontrolled release of pro-inflammatory cytokines, called cytokine release syndrome or "cytokine storm". With increasing severity, not only lungs, but multiple organs are involved, including

spleen and hilar lymph nodes, heart and blood vessels, liver and gallbladder, kidney, adrenal gland, oesophagus, stomach and intestines. A potential participation of the brain and neuroinvasion of SARS-CoV-2 may easily be overlooked in this phase. According to a retrospective case series of 214 COVID-19 patients, up to 36.4% had neurological symptoms manifested as acute cerebrovascular diseases, consciousness impairment and skeletal muscle symptoms [20, 21]. Less severe manifestations are anosmia or, although rarely, ageusia; smell dysfunction are observed in up to 98% of cases [22, 23]. The final stage is accompanied by rapid virus replication, a large number of inflammatory cell infiltration, acute lung injury, acute respiratory distress syndrome (ARDS), extrapulmonary systemic hyperinflammation syndrome with damage of the vascular endothelium, and disseminated intravascular coagulation (DIC) which can progress to gangrene at the extremities and death. This has already been observed before in SARS and MERS [24]. At the very end, the cause of death by the virus is the body's own immune response to the viral infection. Whereas in the first stage of disease anti-viral and supportive treatments are very important, it is evident that at some point during the progress and exacerbation of disease an anti-inflammatory and immunosuppressive intervention can save lives. Virus infection of cells induces oxidative stress: large amounts of highly reactive oxygen species (ROS) are generated in the infected cell, even in the absence of viral replication. This is a common and major pathogenic mechanism for inflammatory response and tissue injury caused by viruses but also by other infectious agents [25, 26]. Oxidative stress is associated with oxidative modifications of proteins, nucleic acids and lipids by free radical chain reactions with catastrophic consequences for a normal molecular functioning within cells. Oxidative stress activates a cascade of inflammatory cytokines, notably IL-1, IL-6, IL-8, IL-12, IFN- γ , IL-18 and TNF, of which IL-6 is a protagonist since it predominately induces pro-inflammatory signalling and regulates massive cellular processes. Janus-kinases significantly contribute to this cytokine-induced pro-inflammatory signalling. Cytokines can stimulate more cytokine production and cause many more cytokine receptors to awaken. Uncontrolled, this becomes a "cytokine storm". Many drugs are known that can interfere with steps of this inflammatory chain reaction such as corticosteroids, cyclosporine, IL-6 inhibitors or Janus-kinase inhibitors (JAK-inhibitors), each having its own mechanism.

Although corticosteroids are known for their anti-inflammatory effects since many decades and have been widely used during the SARS 2003 epidemic in the early acute phase, there is mixed evidence from case series in COVID-19 patients; actually, the WHO does not support their use. Concerns for corticosteroids are that they may delay virus clearance and/or increase the risk of secondary infections [27]. JAK-inhibitors such as baricitinib, ruxolitinib or tofacitinib inhibit autoimmune response to ease inflammation. However, they also inhibit IFN-alpha which is a naturally released cytokine to combat virus infections. A big concern is therefore the decreased resistance to infections. The most preferable treatment method is monotherapy. Among possible side effects JAK-inhibitors may cause anaemia and lymphopenia, although less likely after short exposure. Results of randomised clinical trials for COVID-19 are still lacking. IL-6

inhibitors (e.g., tocilizumab) are monoclonal antibodies that target the pro-inflammatory cytokine IL-6 which is consistently increased in severely ill COVID-19 patients. It is approved in the United States for severe life-threatening cytokine release syndrome and may be an effective treatment also in COVID-19 cytokine storm. Another potential target is the Vascular Endothelial Growth Factor (VEGF); it is responsible for pulmonary oedema and can be suppressed with bevacizumab, a drug, approved by the FDA and widely used in clinical oncotherapy. A naturally occurring substance with a distinctly different mechanism of action is cannabidiol (CBD). Similar to other experimental treatments, it has not yet been used in COVID-19 patients. After almost 50 years of research in man, CBD is recognised as a well tolerated drug with a broad spectrum of activity, and anti-inflammatory, anti-oxidant properties. This has been demonstrated in an animal models of acute lung inflammation [28, 29] and in a viral model of multiple sclerosis (Theiler's murine encephalomyelitis virus-induced demyelinating disease [30], but also in infectious disease models of prion disease [31] and malaria [32]. In another model, CBD reversed oxidative stress parameters, cognitive impairment and mortality in rats submitted to sepsis by coecal ligation and puncture [33]. Instead of acting "downstream" on the cytokine cascade such as IL-6 inhibitors or JAK-inhibitors, CBD is an agonist on peroxisome-proliferator activated receptor gamma (PPAR γ) exerting a dual role as agonist of the nuclear factor erythroid 2 (Nrf2) which plays a key role in cytoprotection against ROS, and as antagonist of the nuclear factor NF κ B which mediates the transcription of pro-inflammatory genes (e.g., those coding for inflammatory cytokines) and proteins such as COX-2 [34, 35]. The induction of the Nrf2 downstream genes is able to protect the infected cells against virus-induced cellular injury. By the same Nrf2 pathway, lung inflammation induced by lipopolysaccharide (LPS) is also alleviated by activation of PPAR γ resulting in improved lung function [28]. CBD inhibits also the VEGF [36]. To note, some patients demonstrated a pathological autoimmune response with high titer of antiphospholipid and other auto-antibodies. At this stage, the initiation of immunosuppressive, anti-inflammation therapy is critical for reducing death rate of COVID-19 patients. Attenuation of oxidative stress and inflammation by a pharmacological measure is therefore highly beneficial for lessening a virus-induced lung injury and exacerbation of existing respiratory diseases [35].

Overall, this means that CBD normalises the physiologic redox balance which is disturbed by the virus-induced cellular injury and restores the self-defence mechanism of the cell. As CBD is a multi-target drug, direct effects on other receptors (GPR55, 5-HT1A, A2A) and on ion channels (notably TRPV1) as well as indirect effects on endocannabinoid levels (notably AEA) that interact on their turn with a number of targets, contribute to the overall restoration and normalisation of physiologic processes in cells [37]. In contrast to IL-6 inhibitors given as example, CBD does not act just on one target but protects the host cells by multiple mechanisms. Simply described, instead of interfering as mailman with receptors, CBD manages the post office. Moreover, because of its chemical structure, CBD has also an immediate direct, strong antioxidant effect exceeding vitamin E and vitamin C, capturing free radicals or transforming them into less active forms. This considerably reduces the destruction of biological

molecules by highly reactive oxygen species (ROS) generated in the virus-infected cell. CBD has already been used in a daily dose of 300mg combined with standard Graft-versus-Host-Disease (GVHD) prophylaxis consisting of cyclosporine and a short course of methotrexate in the prevention of GVHD [38]. In comparison to a historic control group which did not receive CBD, acute GVHD was significantly delayed and tolerance significantly improved. Various animal models demonstrate that doses of 5mg CBD/kg and above are effective as antioxidant. Moreover, CBD easily crosses the blood-brain barrier and is able to combat a potential neuroinvasion of SARS-CoV-2 and neuroinflammation; recently, a case of a patient who was diagnosed with viral encephalitis in Beijing Ditan Hospital has already been described [39]. In addition to mitigating lung inflammation, beneficial effects of CBD have been demonstrated on other aspects related to COVID-19 such as on endothelial cells (vasorelaxation [40], diabetes [41, 42, 43] and stress-induced hypertension [44, 45]. CBD has already been proposed previously as possible treatment for individuals with post Ebola sequelae [46]. All depends on a prompt diagnose and application of such therapy. CBD is safe to use, can be administered already early in the inflammatory phase and can be combined with a large number of other medications such as antibiotics. Recently, a 10% oral solution of CBD containing 7.9% ethanol has received marketing authorisation. Pharmacy preparations based on crystalline CBD can be prepared as capsules (up to 200mg) or as suppositories (up to 300mg) for those patients that need intubation and assisted breathing (e.g., >99.8% phyto-CBD, BSPG Laboratories Ltd, Sandwich, UK or CannPico Research & Marketingservice GmbH, Vienna, Austria). Based on its pharmacological effects and favourable safety profile, CBD of known purity, composition and stability should be considered as a potential treatment for individuals with SARS-CoV-2 infections.

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