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Macrophage responses associated with COVID-19: A pharmacological perspective

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\textbf{ABSTRACT}

COVID-19 has caused worldwide death and economic destruction. The pandemic is the result of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has demonstrated high rates of infectivity leading to great morbidity and mortality in vulnerable populations. At present, scientists are exploring various approaches to curb this pandemic and alleviate its health consequences, while racing to develop a vaccine. A particularly insidious aspect of COVID-19 is the delayed overactivation of the body’s immune system that is manifested as the cytokine storm. This unbridled production of pro-inflammatory cytokines and chemokines can directly or indirectly cause massive organ damage and failure. Systemic vascular endothelial inflammation and thrombocytopenia are potential consequences as well. In the case of COVID-19, the cytokine storm often fits the pattern of the macrophage activation syndrome with lymphocytopenia. The basis for the imbalance between the innate and adaptive immune systems is not clearly defined, but highlights the effect of SARS-CoV-2 on macrophages. Here we discuss the potential underlying basis for the impact of SARS-CoV-2 on macrophages. Here we discuss the potential underlying basis for the impact of SARS-CoV-2 on macrophages, both direct and indirect, and potential therapeutic targets. These include granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 6 (IL-6), interferons, and CXCL10 (IP-10). Various biopharmaceuticals are being repurposed to target the cytokine storm in COVID-19 patients. In addition, we discuss the rationale for activating the macrophage alpha 7 nicotinic receptors as a therapeutic target. A better understanding of the molecular consequences of SARS-CoV-2 infection of macrophages could lead to novel and more effective treatments for COVID-19.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China in December of 2019 and quickly wreaked havoc around the world in the form of the pandemic COVID-19, causing death, undermining medical professionals, and challenging the scientific community (Liu et al., 2020a). This positive-sense single-stranded RNA virus has proven to be highly contagious, being spread by symptomatic and likely asymptomatic individuals (Furukawa et al., 2020; Huff and Singh, 2020; Oran and Topol, 2020). As the name suggests, the primary target of SARS-CoV-2 is the lungs, but other organs such as blood vessels, heart, and brain are susceptible as well. All age groups are vulnerable to infection, but generally exhibit different degrees or classes of symptoms, with those over 60,
male, and with underlying medical conditions more likely to exhibit severe symptoms and succumb to viral toxicity (Conti and Younes, 2020; Team, 2020). Some 81% exhibit mild, moderate, or no symptoms; 14% show severe symptoms; and 5% experience critical disease with high mortality (Wu and McGoogan, 2020). An especially alarming complication of COVID-19 is the cytokine storm that develops after a week or two of delay in severely infected individuals.

SARS-CoV-2 has 4 structural proteins, namely the E (envelope), S (spike), M (membrane), and N (nucleocapsid) proteins (Guo et al., 2020). The N protein holds the RNA genome, while the S, E, and M proteins form the viral envelope. The virus primarily gains entry into a human cell by binding to the exopeptidase angiotensin converting enzyme 2 (ACE2). This protein is located on the membrane surface of several cell types including alveolar type II and endothelial cells. Proteins other than ACE2 may function as receptors for entry as well (Guo et al., 2020). Cell entry is facilitated by cleavage of the spike protein by the serine protease TMPRSS2 or a furin-like proprotein convertase, thereby exposing the fusion peptide. Besides inducing cell death, viral infection can initiate an inflammatory response, which with SARS-CoV-2 is thought to manifest among other things as widespread vascular endothelial dysfunction (Teuwen et al., 2020). Beyond this, however, increasing evidence supports the conclusion that SARS-CoV-2 may exert some of its lethal effects by insidiously compromising the body’s immune response. Here we summarize evidence for macrophages as targets of SARS-CoV-2 and the implication that has for immunomodulatory treatments of COVID-19 (Fig. 1).

2. Cytokine storm

Progression of COVID-19 in more severe cases is marked by the delayed occurrence of a cytokine storm or cytokine release syndrome, due to overactivation of the immune system. Although not definitively established, this phenomenon is thought to contribute to the acute respiratory distress syndrome (ARDS) and widespread organ damage that foretells death. Nor is it clear what relationship there is between the cytokine storm and thrombocytopenia, which is common in patients with COVID-19 and may ultimately contribute to adverse outcome, although both enhanced platelet activation/consumption and destruction are likely outcomes of the cytokine storm. Multi-organ (micro-) thrombosis seems to characterize severe COVID-19 cases (McFadyen et al., 2020; Prieto-Pérez et al., 2020), and likely reflects in part the production of pro-inflammatory cytokines, such as IL-1β and TNF-α, by macrophages (Conti et al., 2020a).

Notably, excessive activation or proliferation of macrophages is a contributing factor to hemophagocytic histiocytosis (HH) also known as secondary hemophagocytic lymphohistiocytosis (Xu et al., 2020). HH has been identified as a deregulation of the immune system, characterized by hemophagocytosis by macrophages, overactivation of cytotoxic T cells, and pro-inflammatory cytokine massive release (Ramos-Casals et al., 2014). HH is the histological counterpart of the macrophage activation syndrome. A clinical study performed on post-mortem bone marrow samples taken from patients who died from COVID-19 showed findings highly consistent with the diagnosis of HH (Prieto-Pérez et al., 2020). Elevated blood ferritin has also been shown to be associated with poor outcome in a retrospective study of 150 COVID-19 patients (Mehta et al., 2020a).

From multiple observations, both CD4+ and especially CD8+ (or cytotoxic) T-cells appear to be over-activated early-on in COVID-19 resulting in the excessive production of granulocyte-macrophage colony-stimulating factor (GM-CSF), which in turn stimulates monocytes/macrophages to produce interleukin-6 (IL-6) and other inflammatory factors. With time, there is a significant decrease in peripheral CD4+ and CD8+ T-lymphocytes, as well as natural killer (NK cells) in COVID-19 patients, perhaps secondarily to their sustained activation by macrophage-derived interferon gamma-induced protein 10 (IP-10), also known as CXCL10. With disease progression, neutrophilia may occur,
especially in those with severe critical pulmonary conditions (Liu et al., 2020).

3. Macrophage (monocytes)

3.1. Inflammatory signature

Human monocytes and macrophages express ACE2, as well as TMPRSS2 and furin, and would seem to be a widespread target for SARS-CoV-2 infection (Abassi et al., 2020; Wang et al., 2020b). Evidence was reported in COVID-19 patients for the infection of macrophages of the CoV-2 infection (Abassi et al., 2020; Wang et al., 2020b). Moreover, infected macrophages were shown to produce IL-6, a pro-inflammatory cytokine that directly promotes lymphocyte necrosis and would explain in part the common characteristic of lymphocytopenia in COVID-19 patients. Based on their morphology and ability to produce IL-6, TNF-α, and IL-10, as well as surface expression of CD11b, CD14, CD68, CD80, CD163, and CD206, circulating monocytes have an activated or pro-inflammatory phenotype. The expression of CD163 and CD206 suggests a bias towards the intermediate or regulatory phenotype, with CD163 expression being a feature of activated monocytes/macrophages in hemophagocytic lymphosistiocytosis syndrome (Wang et al., 2020b). An increase in the pool size of the intermediate subtype of monocytes may be characteristic of severe COVID-19 (Merad and Martin, 2020). The activated plasma blood monocyte phenotype and lymphocytopenia would seem to persist into the recovery stage as well (Wen et al., 2020).

Multiple studies have demonstrated that the lungs are a target of macrophages in COVID-19 (Chua et al., 2020; Wang et al., 2020b). Inflammatory macrophages are increased with increased levels of nonresident macrophages, which in the upper respiratory tract have a highly inflammatory phenotype with the expression of a number of chemokines and pro-inflammatory cytokines IL-1β, IL-8, IL-18, and TNF-α (Chua et al., 2020; Liao et al., 2020). Macrophages in the lower airways were found to have an even stronger inflammatory signature and overall there was a strong correlation between activation status of non-resident macrophages and COVID-19 disease severity (Chua et al., 2020). Other immune cells, such as mast cells, likely act synergistically with macrophages to cause lung damage (Kritas et al., 2020).

3.2. Interferon suppression

Although CXCL10, as well as CCL2, are interferon (IFN)-induced genes, there is evidence for impaired or delayed Type 1 IFN signaling in SARS-CoV-2-infected cells. One ex vivo experiment with lung tissue showed that SARS-CoV-2 induced less IFNs and pro-inflammatory mediators than SARS-CoV (Chu et al., 2020). Single-cell RNA sequencing analysis of bronchoalveolar lavage samples from severe and mild COVID-19 patients revealed that SARS-CoV-2 mainly infects the epithelial and recruited inflammatory macrophage subsets (Bost et al., 2020). In the latter, a disease severity-associated downregulation of type I IFN genes was noted. Notably, IFN is known to exhibit multiple biological functions such as antiviral, antiproliferative, and immunomodulatory effects (Nile et al., 2020; Wang et al., 2019). How SARS-CoV-2 thwarts intrinsic innate immune responses in monocyte-macrophages is not defined, although in monocyte-derived dendritic cells (but not macrophages) viral antagonism of STAT1 phosphorylation was reported (Yang et al., 2020). In contrast, work in Vero cells, indicates that SARS-CoV-2-infected cells are still responsive to type I IFN treatment unlike SARS-CoV-infected cells (Izukugame et al., 2020). Of note, ACE2 was shown to be an interferon-stimulated gene in human lung cells, which is also upregulated by smoking and viral infections (Smith et al., 2020). A discussion of possible means by which SARS-CoV-2 attenuates the interferon response can be found elsewhere (Paces et al., 2020). Recently, it was reported that the SARS-CoV-2 viral ORF6, ORF8 and N proteins were potential inhibitors of the type I interferon signaling pathway (Li et al., 2020).

In light of these observations and urgent need to identify new therapies to control COVID-19 severity, IFN approved drugs have emerged as a potential treatment for COVID-19 patients. For instance, it has been demonstrated that the administration of recombinant IFNs to SARS-CoV and SARS-CoV-2 patients decreased viral protein synthesis and replication (Faldarano et al., 2013; Li et al., 2019; Zumla et al., 2016). In agreement, a recent published study on MERS-CoV patients reported that a combination of remdesivir and IFN beta showed a superior antiviral effect when compared with lopinavir/ritonavir combination (Sheahan et al., 2020). Therefore, testing the efficacy and safety of recombinant IFNs may be a worthwhile promising approach in the setting of COVID-19. Triple antiviral therapy with lopinavir-ritonavir, ribavirin and interferon beta-1b was reported to be safe and superior to lopinavir-alone in improving symptoms and reducing viral shedding and hospitalization in those with mild to moderate COVID-19 (Hung et al., 2020). On the other hand, there is evidence that IFN might be playing an important role in COVID-19 hyper-inflammation, suggesting that timing is a consideration (Conti et al., 2020c; Lee et al., 2020). Analysis of monocytes by single-cell RNA-seq from patients with severe COVID-19 exhibited signs of a type I IFN response along with TNF/IL-1β-driven inflammation.

3.3. Possible contribution of nicotine and nicotinic acetylcholine receptors

Although multiple investigations report a detrimental impact of nicotine on COVID-19 patients through up-regulating ACE2 receptors in the lungs (Farsalinos et al., 2020; Leung et al., 2020; Russo et al., 2020), recently published epidemiological studies reveal that smokers are either asymptomatic or show less severe respiratory symptoms compared with non-smokers (Covid et al., 2020; Farsalinos et al., 2020b; Kloc et al., 2020; Miyara et al., 2020; Pettrilli et al., 2020). A disruption of the cholinergic anti-inflammatory pathway in COVID-19 patients has been noted (Farsalinos et al., 2020a, 2020c). It has been reported that over-responsiveness of the immune system, otherwise known as the cytokine storm, highly correlates with enhanced severity of COVID-19 infection, substantially increasing the mortality rate (Wang et al., 2020a; Ye et al., 2020). In the human lungs, the inflammatory response is mainly mediated by lung macrophages with two main types: the alveolar and interstitial macrophages (Kloc et al., 2020). Under physiological conditions, the alveolar macrophages exhibit anti-inflammatory characteristics by dampening the adaptive immune response and suppressing pro-inflammatory cytokines release (Kloc et al., 2020). Following a viral infection such as COVID-19, the alveolar macrophages switch from the anti- to pro-inflammatory phenotype, initiating consequently an inflammatory response, then switch back during the resolution phase to the anti-inflammatory phenotype, promoting thereafter tissue repair in the site of injury (Hu and Christmas, 2019; Russell and Bell, 2014). In the context of COVID-19 infection, an accumulation of macrophages in the lungs of COVID-19 patients has been observed (Wang et al., 2020a). Besides resident macrophages, monocyte-derived and non-resident macrophages have been described in COVID-19 patients (Chua et al., 2020); however, a better understanding of their interrelationship is needed.

Of note, lung macrophages have been shown to express ACE2 receptors, facilitating therefore the entry of SARS-CoV-2 to host cells (Tsaytler et al., 2011; Verdecchia et al., 2020). Besides ACE2 receptors, lung macrophages express alpha 7 nicotinic receptors (nAChRs α7) (Abrial et al., 2012). nAChRs α7 are potentially implicated in attenuating the cytokine storm through decreasing pro-inflammatory cytokine release (Kalamida et al., 2007; Tracey, 2002). For instance, it has been indicated that activation of nAChRs α7 located on lung macrophages by acetylcholine and/or nicotine mitigates the hyper-inflammatory response mediated disease severity (Tu et al., 2014; Tindle et al., 2020). Strong evidence reveals that the cholinergic anti-inflammatory pathway mediated by nAChRs α7 inhibits the translocation of the
pro-inflammatory marker NF-κB to the nucleus and activates the JAK2-STAT3 pathway, consequently suppressing the inflammatory response and decreasing the cytokine storm in the lungs (Báez-Pagán et al., 2015; Changeux et al., 2020; Lu et al., 2014). Given the observed lower number of hospitalized COVID-19 patients among smokers, the potential role of medicinal nicotine to alleviate COVID-19 progression and development should be rapidly studied and clearly distinguished from conventional smoking that has no therapeutic effects.

3.4. Chemokine profile: a possible role for CXCL10 (IP-10)

Longitudinal profiling of 71 COVID-19 patients identified early expression of inflammatory mediators IL-10 and IL-1RA, along with the chemokine CCL5 (aka RANTES), in those with mild but not severe disease (Zhao et al., 2020). CCL5 is chemotactic for T cells, as well as eosinophils and basophil. On the other hand, the majority of cytokines associated with the cytokine storm in viral infections, including IL-6 and IFN-γ, were only increased at a late stage in severe illness, with TNF and GM-CSF not showing a difference between mild and severe cases.

Multiple studies have documented the upregulation of not only inflammatory cytokines but also chemokines in COVID-19 patients. Chemokines are low molecular weight proteins that act largely as chemoattractants for immune cell recruitment during inflammation, as well as modulators of immune cell homeostasis and angiogenesis (Coperchini et al., 2020). Compared to non-ICU patients, COVID-19 patients admitted to the ICU, exhibited higher plasma levels of IL2, IL7, IL10, GSCF, CXCL10 (IP-10), CCL2 (MCP1), CCL3 (MIP1A), and TNFα, indicating activation of T-helper 1 (Th1) cell function (Huang et al., 2020), although increased circulating levels of Th2-immune related cytokines IL-4 and IL-10 implicated in inflammation suppression are noted as well (Han et al., 2020). Transcriptomic analysis of bronchoalveolar lavage fluid of COVID-19 patients revealed an upregulation of CXCL1, CXCL2, CXCL6, CXCL8 (IL8), CXCL10 (IP-10), CCL2 (MCP-1), CCL3 (MIP-1A), and CCL4 (MIP1B) (Xiong et al., 2020). CXCL10 (IP-10) is a chemoattractant for monocytes/macrophages, dendritic cells, NK cells, and T cells; CCL2 (MCP-1) is a chemoattractant for monocytes, dendritic cells, and memory T cells. CXCL2 and CXCL8, which are secreted by monocytes/macrophage, serve as potent chemotactic agents for neutrophils. Single cell RNA sequencing of nasopharyngeal and bronchial samples from COVID-19 patients identified increased inflammatory macrophages that express CCL2, CCL3 (MIP-1A), CCL20, CXCL1, CXCL3, CXCL10 (IP-10), CXCL8 (IL8), IL1B and TNF-α (Chua et al., 2020). Levels correlated with disease severity. CXCL10 (IP-10) levels were previously associated with the severe acute respiratory syndrome (SARS) disease progression and resolution due to the SARS-CoV virus (Altara et al., 2016; Jiang et al., 2005), and development of ARDS in preclinical models (Coperchini et al., 2020). The elevated nasopharyngeal levels of CXCL10 with COVID-19 may permit this chemokine to be used in widespread immunoassay testing for early detection of SARS-CoV-2-infection (Cheemarla et al., 2020).

3.5. Possible contribution of GM-CSF

Mounting evidence suggests that immunomodulatory agents, including GM-CSF, could be a promising therapy for COVID-19 (Lang et al., 2020; Mehta et al., 2020a). GM-CSF is known to be implicated in the production of granulocytes, monocytes, macrophages, and dendritic cells from progenitor cells, a process known as myelopoiesis (Egen et al., 2010; Fleetwood et al., 2007). It has been demonstrated that GM-CSF is secreted by different cell types including alveolar type II epithelial cells, playing therefore a key role in the integrity of alveolar barriers and maturation of alveolar macrophages (Cakirova et al., 2005; Roasler and Herold, 2016). Multiple investigations have considered GM-CSF as a pivotal cytokine that activates both the innate and adaptive immune response. For instance, GM-CSF can polarize myeloid cells into a pro-inflammatory phenotype, releasing subsequently reactive oxygen species and pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and chemokines including CCL17, CCL2, and IL8, which can attract lymphocytes, monocytes, and neutrophils to the site of inflammation (Hamilton, 2020). It has also been reported that GM-CSF can prime dendritic cells to activate T cells, boosting thereafter the immune response by enhancing the recruitment of myeloid cells to the site of injury (Cao et al., 2015; Komuzcki et al., 2019; Zhang et al., 2013). Since the goal of enhancing lung tissues integrity and dampening hyper-active immune response may lead to a drastic decrease in morbidity and mortality rate in COVID-19 patients, administration of GM-CSF as a promising therapy is being clinically investigated (Lang et al., 2020).

Pre-clinical investigations revealed that overexpression of GM-CSF decreased apoptosis in alveolar wall cells, consequently preventing hypoxia-induced lung damage (Baleeiro et al., 2006; Paine et al., 2003). A clinical study performed by Matute-Bello et al. reported that in ARDS patients, increased GM-CSF in bronchoalveolar lavage fluid was associated with decreased mortality rate through potentially improved alveolar macrophage survival (Matute-Bello et al., 2000). This observation was further strengthened with a clinical study completed by Herold et al. showing that administration of inhaled GM-CSF to patients with pneumonia-associated ARDS enhanced oxygenation and lung compliance (Herold et al., 2014). Currently, a clinical study is assessing the potential beneficial effect of using inhaled and intravenous GM-CSF agonist in respiratory failure COVID-19 patients (NCT04400929).

The potential benefits of administering GM-CSF agonist in the context of COVID-19 patients, however, should be carefully studied, particularly in the late stage of COVID-19 where lung injury is thought to be driven by the cytokine storm rather than viral overload ( Siddiqi and Mehra, 2020). Paradoxically, considerable interest in administering anti-GM-CSF is gaining interest in the setting of COVID-19, given that a marked increase in GM-CSF expressing natural killer, B cells, and CD4+ and CD8+ T cells was observed in COVID-19 ICU patients when compared to mild cases (Zhou et al., 2020). However, given the role of GM-CSF in boosting the immune response to remove pathogen and enhancing lung repair, it is important to consider that the observed increase could be a result of exacerbated COVID-19 severity and related comorbidities. The rational is that during COVID-19 infection, over-activation of myeloid cells could be a critical mediator of enhanced cytokine storm, consequently aggravating tissue damage. Therefore, anti-GM-CSF therapy may decrease the detrimental immune response, and thus exert beneficial effects (Barnes et al., 2020a; Mehta et al., 2020a; Merad and Martin, 2020), a hypothesis that was supported by a preclinical study of SARS-CoV infection animal model, showing that GM-CSF mediated the infiltration of inflammatory monocytes/macrophages into the lungs (Channappanavar et al., 2016). Taking together, these findings suggest that GM-CSF is a key player in regulating myeloid cell induced hyper-inflammation in many tissues including the lungs. Anti-GM-CSF approach in patients with COVID-19, however, should be well monitored, given the critical contribution of GM-CSF in alveolar macrophage function and pathogen clearance.

As of the start of May 2020, there were some 49 clinical trials underway targeting the cytokine storm in COVID-19 patients (Wang et al., 2020b). The vast majority involve biologicals. Besides those involving GM-CSF, prominent among them are a number of studies involving anti-IL-6 strategies. In addition, antagonistic antibodies directed against TNF, IL-1, IL-1R, and IL-8 are being investigated for attenuating excessive immune activation and the cytokine storm (Conti et al., 2020b). The rationale behind those targeting the actions of GM-CSF in COVID-19 is that this cytokine constitutes an autocrine/paracrine positive feedback loop that helps drive the cytokine storm (Mehta et al., 2020b). In a preliminary study, dexamethasone showed promise in reducing mortality of hospitalized COVID-19 patients if they were receiving respiratory support (mechanical ventilation or oxygen) (Group et al., 2020), but targeting the cytokine storm via broad-spectrum immunosuppression does raise a number of concerns (Theoharides and Conti, 2020).
3.6. Possible contribution of the renin angiotensin system

SARS-CoV-2 can gain entry into monocytes/macrophages via ACE2, although the virus is not thought to replicate in these cells. In this way, macrophages may act as sort of “Trojan horse”, allowing for the delivery of the virus to lung and other tissue parenchyma (Abassi et al., 2020). ACE2 is a protease that forms part of the beneficial counterpoint to the renin-angiotensin system (Forrester et al., 2018). By removing the carboxy-termius amino acid, it converts the vasoconstrictive and pro-inflammatory octapeptide angiotensin II (Ang II) to Ang (1–7), which has beneficial effects including vasodilatation and anti-inflammation actions via the Mas receptor.

An additional consequence of virus-mediated ACE2 loss might be increased Ang II inflammatory effects via the Ang II type 1 (AT1) receptor or diminished protective signaling via the Mas receptor (Abassi et al., 2020). Although multiple studies reported increased ACE2 expression in COVID-19 patients who are on angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) (Ferrario et al., 2005; Igase et al., 2008), recent emerging investigations suggested that ACEIs and ARBs could exert protective effects through up-regulating ACE2, modulating negatively therefore the severity of COVID-19 (Kuba et al., 2005) and reversing the marked increase in Ang II levels, decreasing consequently its deleterious effects on the cardio-pulmonary system (Danser et al., 2020; Sommerstein et al., 2020; Zheng et al., 2020). A study done by Kuba et al. showed that the administration of exogenous ACE2 to ARDS animal model substantially decreased inflammation and enhanced oxygenation (Kuba et al., 2005). Similarly, epidemiological studies revealed that ACEIs and ARBs decreased the risk of pneumonia in general population (Liu et al., 2013; Shinohara and Altarac, 2012). Therefore, investigation aimed at testing the potential beneficial or detrimental effects of ACEIs and ARBs in the context of COVID-19 is being undertaken (Buckley et al., 2020).

4. Conclusions

Substantial evidence indicates that pro-inflammatory macrophages play a critical role in the pathological consequences of COVID-19. Additional evidence is needed concerning the phenotype of these cells. Nor is it clear what the relationship is between SARS-CoV-2 infection and monocyte/macrophage activation status, namely whether these immune cells are simply responding to the viral infection or are hijacked by the virus to act in an uncontrolled rogue manner. Emerging evidence indicates that targeting the cytokines and chemokines associated with their activation or restoring their innate immunity control may provide the means to successfully combat COVID-19.

Author agreement

Our work is original, written based on the most recent studies and discoveries, and is being submitted only to European Journal of Pharmacology, has not been published already, and is not under consideration for publication or in press elsewhere. All authors agree to the submission of the manuscript.

Dedication

This manuscript is dedicated to G. Warren and Jessie Booz, two gentle, loving, caring, and gifted individuals, and all of those wonderful and remarkable individuals who were taken from us way too soon by the COVID-19 pandemic.

CRediT authorship contribution statement

George W. Booz: Writing - review & editing, All authors contributed to the writing of this manuscript. Raffaele Altara: modified the figure and provided assistance in producing a high quality TIFF, All authors contributed to the writing of this manuscript. Fouad A. Zouein: Writing - review & editing, coordinated the author contributions, All authors contributed to the writing of this manuscript.

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