Anti-Inflammatory Properties of Drugs Used to Control COVID-19 and their Effects on the Renin-Angiotensin System and Angiotensin-Converting Enzyme-2

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ABSTRACT-COVID-19 infection is associated with systemic inflammation, and sometimes hyperinflammatory responses with cytokine storm. This plays a major role in COVID-19 severity and poor disease prognosis, even death. Higher levels of inflammatory hallmarks including C-reactive protein, ferritin, D-dimers, and cytokines such as interleukin (IL) -6, IL-10 and tumor necrosis factor- α (TNF-α) have been reported. Many anti-viral drugs have been tried, but none were proven fully effective. Supportive care and management of the complications that are caused mainly by inflammation might be the key to greater survival rates and shorter hospitalization (e.g., the use of remdesivir, lopinavir, ritonavir, umifenovir (arbidol), oseltamivir, ganciclovir, favipiravir, darunavir, hydroxychloroquine, chloroquine, colchicine, azithromycin, anakinra, canakinumab, tocilizumab, siltuximab, sarilumab, Type 1 interferon, interferon β-1a, interferon α-2b, baricitinib, ruxolitinib, fedratinib, methylprednisolone and dexamethasone). However, the efficacy of these treatments still needs well-planned clinical trials. In such trials, careful attention must be paid to the duration of the treatment, the onset of beneficial effects, and the severity of the disease, otherwise, the outcomes may still remain inconclusive. Herein, we present a review of the current drugs, which are being used in the management of the disease and their anti-inflammatory properties. We also investigated if these drugs directly interact with Angiotensin-Converting Enzyme (ACE 2), which is a crucial component of the virus entry to the cells.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a viral infection caused by a new β-coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is an enveloped non-segmented positive-sense RNA virus (1-4).

COVID-19 is an acute respiratory infectious disease, which primarily spreads through the respiratory tract (3, 5, 6). The virus can be transmitted through the spread of droplets from patients to others or oral-fecal route (7-9). The common clinical symptoms of COVID-19 infection include cough and fever as the dominant symptoms, shortness of breath, fatigue, increased sputum production, sore throat, and headache. Additionally, up to 5 percent of the patients show gastrointestinal symptoms including diarrhea and vomiting (10-14).

In most cases, patients who develop acute respiratory distress syndrome are elderly patients or those with underlying disorders such as hypertension, chronic obstructive pulmonary disease, diabetes, and cardiovascular complications. Other symptoms include septic shock, metabolic acidosis, and coagulation dysfunction, which may lead to death (11-16).

Covid-19 infection is associated with systemic inflammation, as do other infections. It has been shown that in several viral infections such as hepatitis C virus, HIV, hepatitis B virus, influenza virus, and severe acute respiratory syndrome virus (SARS-CoV), inflammation exists and levels of

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ABBREVIATION - ACE 2, Angiotensin-Converting Enzyme II; **AT**, Angiotensin receptor; **COVID-19**, coronavirus disease 2019; **CRS**, cytokine release syndrome; **FDA**, the U.F, Food and Drug Administration; **GCSF**, granulocyte colony-stimulating factor; **IL**, interleukin; **HIV**, human immunodeficiency viruses; **ICU**, intensive care unit; **IP-10**, interferon-gamma-induced protein; **JAK**, Janus Kinase; **MCP-1**, monocyte chemoattractant protein-1; **MIP-1α**, macrophage inflammatory protein 1-α; **RAS**, Renin-Angiotensin System; **SARS-CoV-2**, severe acute respiratory syndrome coronavirus 2; **TNF-α**, tumor necrosis factor-α

interleukin (IL) -6 and tumor necrosis factor-α (TNF-α) are increased (17-19). The laboratory results indicate that in most COVID-19 patients white blood cell count is normal or decreased, and lymphocytopenia exists (12-14, 16). In severe cases, the neutrophil count, D-dimer, blood urea, and creatinine levels are significantly higher than normal ranges, and the lymphocyte counts decrease. Moreover, inflammatory biomarkers such as IL-6, IL-10 and TNF-α) increase in COVID-19 patients, which is an indication of the inflammation associated with COVID-19 (12, 20-22). The ICU patients also had higher plasma levels of IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (GCSF), 10 kD interferon-gamma-induced protein (IP-10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1-α (MIP-1α) (4). The hypersecretion of the cytokines, also known as "cytokine storm", is associated with the disease severity (21, 23-25). Additionally, it has been reported that the C reactive protein (CRP), a commonly used inflammatory marker in clinical practice, is significantly higher in severe cases of COVID-19 as compared to non-severe cases (26).

Several studies have already published to frame how hyperinflammatory responses, which resemble the cytokine release syndrome (CRS), play a major role in COVID-19 severity and usually associated with poor disease prognosis (21, 23-25). Higher levels of inflammatory hallmarks including C-reactive protein, ferritin, D-dimers, and cytokines such as IL-6, IL-10, and TNF-α consistently occur in patients with CRS (4, 26, 27).

In general, inflammation is a fundamental and protective reaction of the body to infections and injuries, which has very complex and diverse patterns and has a significant role in the development of various diseases (28, 29). There are two types of inflammatory responses, acute and chronic. During acute inflammation, leukocytes infiltrate the damaged region to remove the stimulus and repair the tissue. This process results in healing in a short time. On the other hand, chronic inflammation is a prolonged and dysregulated process, which involves active inflammation and tissue destruction. Chronic inflammation is associated with many pathophysiological conditions such as atherosclerosis, cancer, arthritis, and autoimmune diseases (29). Inflammation often is associated with altered expression of metabolizing enzymes, transporters, receptors, and plasma proteins (30).

In some cases, the immune response that is triggered by SARS-CoV-2 goes out of control so that it may lead to pulmonary tissue damage, functional impairment, and reduced lung capacity (31). Although much of the attention has been paid to pulmonary complications, it is important to also focus on other pathophysiological aspects of COVID-19 such as cardiovascular complications. Cardiovascular events associated with COVID-19 are significant contributors to the mortality of the disease and include but not limited to myocardial injury and myocarditis, acute myocardial infarction, acute heart failure and cardiomyopathy, dysrhythmias (32-34), and thromboembolic events (35). Most of these complications are due to severe systemic inflammation that increases the risk of cardiovascular or other organ complications (22, 32). Arguably, female patients may be more tolerant of the complication of COVID-19 infection due to the anti-inflammatory actions of estrogen (36).

In addition, SARS-CoV-2 enters the lung alveolar epithelial cells through a receptor-mediated endocytosis mechanism. The virus utilizes the angiotensin-converting enzyme II (ACE2) as the entry receptor. The spike (S) protein of SARS-CoV-2 binds to Angiotensin-Converting Enzyme II (ACE 2), which leads to virus entry to the host cell. The virus uses the cellular protease

TMPRSS2 (transmembrane protease serine 2) for priming the spike protein and its activation (37-39).

The Renin-Angiotensin System (RAS) regulates human physiology and controls cardiovascular homeostasis. The RAS exerts its effects through its components, the angiotensin-converting enzyme (ACE) and ACE2, their angiotensin (Ang) products (Ang II and Ang1-7), Ang II receptor type 1 (AT1R) and type 2 (AT2R) and G-coupled protein receptor of Ang1-7, Mas receptor. ACE metabolizes Ang I to Ang II which binds with AT1R and AT2R. RAS consists of two opposing arms. The first arm, ACE, Ang II, and AT1R causes inflammation, vasoconstriction, cell proliferation, and fibrosis. The second arm is anti-inflammatory, antifibrotic, antiproliferative, and a vasodilator. It consists of ACE2, Ang1-7, and Mas receptor An imbalance of RAS components changes the system's role from a regulator to a harmful one (40-42). Inflammation causes such an imbalance (30, 43, 44), and being an inflammatory condition, COVID-19 seems to do the same (45).

To treat COVID-19 patients, various pharmacological interventions are suggested. The evidence to support beneficial effects is, however, mainly questionable (46). This review was carried out to test the hypothesis that the majority of drugs proposed to treat COVID-19 are anti-inflammatory in nature. Currently, there are no Food and Drug Administration (FDA)-approved drugs for the treatment of COVID-19, although remdesivir, which is an investigational antiviral drug is available through an FDA emergency use authorization (47-50). Other antiviral drugs such as a combination of lopinavir and ritonavir (47, 51, 52) and favipiravir (47, 53) have been also used in the treatment of COVID-19. However, in all cases, the FDA panel recommended against using them because solid clinical trial data are absent or no significant clinical benefit has been observed in patients with COVID-19.

METHODS

Search and selection strategy

Initial serch to identify the drug classes in the treatment of COVID-19

Since there are overwhelming number of the publications in regards to the treatment of COVID-19, initially we conducted a search to identify the drug classes which are mostly used in the treatment of the disease. The search was conducted using keywords "COVID-19" AND "Treatment" OR "Management" OR "Drug class" in PubMed and ScienceDirect databases and the US clinical trials registry (https://clinicaltrials.gov/ and https://www.covid19treatmentguidelines.nih.gov/whats-new/). The initial search helped us to identify our keywords for step 1. For articles not in English, we used the web version of the Google Translate (https://translate.google.com/)

Step 1: identification of the drugs used in the treatment of COVID-19

We search for medications used to treat COVID-19 patients during January 1, to July 14, 2020 under the class of drugs identified in the initial search using the mentioned databases. Keywords consisted of "COVID-19" AND each of the following terms: "antiviral treatment", "macrolide", "antimalarial", "interleukin-1 (IL-1) inhibitor", "interleukin-6 (IL-6) inhibitor", "interferon treatment", "Janus Kinase (JAK) inhibitor", and "corticosteroid therapy". After trying several different combinations, the search keywords were selected among different possible combinations to find the most relevant results. Moreover, missing publications were identified by going through the reference lists of the selected articles. The articles that studied the current pharmacological options for the treatment of COVID-19 were selected for this review. Duplicates were excluded from the search results. For reporting the step 1 results, the name and category of the drugs, main therapeutic use, the mechanism(s) of action for the main therapeutic use, and references were presented. Figure 1 summarizes the study selection design for step 1.

Step 2: reviewing the anti-inflammatory properties of the drugs identified in step 1 and their possible effect on ACE2

We searched each drug, which was identified in step one for their anti-inflammatory properties and their possible effect on activation or inhibition of the ACE2. PubMed and ScienceDirect databases were selected as the search tools. Keywords for the

search included “The name of the drug identified in step 1” AND “anti-inflammatory” or “The name of the drug identified in step 1” AND “ACE 2”. The search conducted without any language or time restriction to identify the maximum number of published studies. Moreover, missing publications were identified by going through the reference lists of the selected articles. Duplicates were excluded from the search results.

RESULTS

From our initial search the following keywords was selected for the main serch in step 1: “COVID-19” AND each of the following terms: “antiviral treatment”, “macrolide”, “antimalarial”, “interleukin-1 (IL-1) inhibitor”, “interleukin-6 (IL-6) inhibitor”, “interferon treatment”, “Janus Kinase (JAK) inhibitor”, and “corticosteroid therapy”.

In total, 1066 articles were found and screened and among those, 62 were selected based on the inclusion criteria (Figure 1).

Table 1 lists the drugs, which were identified as the current or potential pharmacotherapies for the treatment/management of COVID-19.

With the exception of a few, drugs used in treating COVID-19 infection have either direct or indirect anti-inflammatory actions (Table 2).

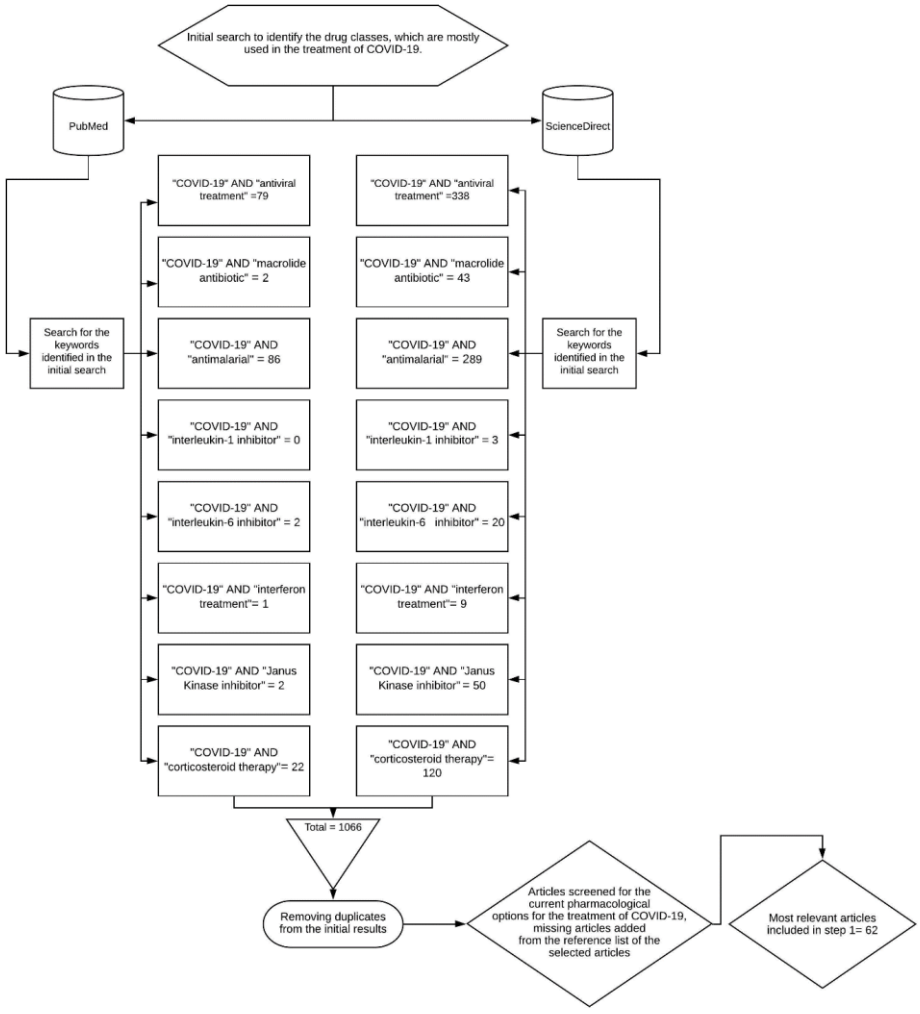

Figure 1. Summary of the study design for step 1.

Table 1. Drugs used to treat COVID-19 infection

Drug	Main use	Mechanism(s) of action for the main therapeutic use	Reference(s)
Remdesivir	Antiviral	Adenosine nucleotide prodrug	(47-50, 54-58)
Lopinavir, ritonavir	Antiviral	Protease inhibitor	(47, 48, 51, 52, 59-61)
umifenovir (arbidol), oseltamivir, and ganciclovir	Antiviral	Umifenovir inhibits membrane fusion. Oseltamivir is a neuraminidase inhibitor. Ribavirin is a nucleoside inhibitor and a polymerase inhibitor. Ganciclovir inhibits viral DNA polymerase	(56, 61)
Favipiravir	Antiviral	Selective inhibition of viral RNA-dependent RNA polymerase.	(53)
Darunavir	Antiviral	Protease inhibitor	(62)
Hydroxychloroquine, chloroquine	Anti-malaria agent. Immunomodulator to treat autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis	Exact antimalarial mechanism of action is unknown, possibly by raising intracellular pH, and, affecting the endosomal activity	(58, 63-71)
Colchicine	Gout, Familial Mediterranean Fever	Colchicine modulates multiple pro- and antiinflammatory pathways associated with gouty arthritis, including prevention of microtubule assembly, which in turn disrupts the inflammasome activation, microtubule-based inflammatory cell chemotaxis, generation of leukotrienes and cytokines, and phagocytosis	(72-74)
Azithromycin	Macrolide antibiotic	Binds to 50S ribosomal subunit of microorganisms	(58, 65, 71, 75, 76)
Anakinra	Rheumatoid arthritis	Interleukin-1 inhibitor	(55, 77, 78)
Canakinumab	Cryopyrin-associated periodic syndromes	Interleukin-1 inhibitor	(79)
Tocilizumab	Rheumatoid arthritis, cytokine release syndrome	Interleukin-6 inhibitor	(80-86)
Siltuximab	Castleman Disease	Interleukin-6 inhibitor	(80, 87, 88)
Sarilumab	Rheumatoid arthritis	Interleukin-6 inhibitor	(58, 89, 90)

Table 1, Cont'd

Type 1 interferon (IFN–I), mainly Interferon β-1a, and Interferon α-2b	Multiple Sclerosis, hepatitis B/C, hairy cell leukemia melanoma	Interferon binds to interferon receptors. Immunomodulator	(56, 57, 61, 91-94)
Baricitinib	Rheumatoid arthritis	Janus Kinase inhibitor	(54, 57, 95-99)
Ruxolitinib	Myelofibrosis	Janus kinase inhibitor	(54, 100-102)
Fedratinib	Myelofibrosis	Janus kinase inhibitor	(103)
Methylprednisolone	Several, including allergic conditions, acute exacerbation of multiple sclerosis, acute spinal cord injury	Corticosteroid	(58, 104-106)
Dexamethasone	Several, including general inflammation, acute exacerbation of multiple sclerosis, cerebral edema, shock, allergic conditions	Corticosteroid	(25, 54, 59, 107, 108)

Table 2. Anti-inflammatory properties of the drugs used in the treatment of COVID-19 and their potential mechanisms.

Drug	**Direct or indirect Anti-inflammatory effect**	**Direct effect or interaction with ACE 2**
Remdesivir	Indirect[1]	Indirect[2]
Lopinavir, ritonavir	Indirect[1]	Indirect[2]
Umifenovir (arbidol), interferon, oseltamivir, ribavirin, and ganciclovir	Indirect[1], also oseltamivir prophylaxis may reduce inflammation and facilitate cross-strain protective T cell memory to influenza virus (109). Anti-inflammatory effect of macromolecular pro-drugs of ribavirin is attributed to the polymer bckbone of the pro-drugs, not the drug aloane (110).	Indirect[2]
Table 2, Cont'd		
Favipiravir	Indirect[1]	Indirect[2]
Darunavir	Indirect[1]	Indirect[2]
Hydroxychloroquine, Chloroquine	Direct. Inhibition of IL-1-alpha production by monocytes and IL-6 production by T cells and monocyte Inhibition of the alkaline cytosolic lysophospholipase and phospholipase A inhibition of T and B-cell receptors calcium signaling, inhibits toll-like receptors signaling, and inhibition of tumor necrosis factor (TNF)-alpha production (68, 111-124).	May prevent the viral S protein from binding to a newly discovered ganglioside-binding domain,

Table 2, Cont'd		
		which is located at the tip of the N-terminal domain of the SARS-CoV-2 S protein (183)
Colchicine	Direct. Distruption the cytoskeletal functions through inhibition of β-tubulin polymerization into microtubules, which in turn prevents activation, degranulation, and migration of neutrophils. It may interfere with intracellular assembly of inflammasome complex in neutrophils and monocytes, which mediates the activation of interleukin-1β (125-127).	Indirect[2]
Azithromycin	Direct. Reducing the expression of iNOS and the pro-inflammatory macrophage receptor (CCR7) and polarizing Macrophages to an M2 Phenotype by Inhibition of the STAT1 and NF-κB signaling pathways. Interactions with cytosolic phospholipase A 2 ($cPLA_2$) results in inhibiting PGE_2, IL-6, IL-12p40, and arachidonic acid release, increased endocytosis and/or expression of Toll- like receptor (TLR)2, TLR4, and TLR9 in dendritic cells (DCs), inhibition of production of pro-inflammatory cytokines – such as IL-8, IL-6, TNF alpha, and MMPs (128-132).	Indirect[2]
Anakinra	Direct. Interleukin-1 receptor antagonist (133).	Indirect[2]
Canakinumab	Direct. Interleukin-1 receptor antagonist (134-137).	Indirect[2]
Tocilizumab	Direct. Interleukin-6 receptor antagonist (138-142).	Indirect[2]
Siltuximab	Direct. Interleukin-6 receptor antagonist (140, 142, 143).	Indirect[2]
Sarilumab	Direct. Interleukin-6 receptor antagonist (144-146).	Indirect[2]
Interferon β-1a, Interferon α-2b	Direct. Binding to specific receptors on the cell membrane and trigger the JAK-STAT signaling pathway. Enhance macrophage, cytotoxic T cell, and natural killer cell activity (118, 147-154).	Indirect[2]
Baricitinib	Direct. Inhibitor of the Janus kinases (155-159).	Indirect[2]
Ruxolitinib	Direct. Inhibitor of the Janus kinases (101, 159-161).	Indirect[2]
Fedratinib	Direct. Inhibitor of the Janus kinases (103, 159, 162)	
Methylprednisolone	Direct. Suppress inflammation by several mechanisms. Corticosteroids enter the cell to bind to Glucocorticoid	Indirect[2]

Table 2, Cont'd

	receptor in the cytoplasm that translocates to the nucleus, switching off the inflammatory genes (163-167).	
Dexamethasone	Direct. Suppressing inflammation by several mechanisms. Corticosteroids enter the cell to bind to Glucocorticoid receptor in the cytoplasm that translocates to the nucleus, switching off the inflammatory genes (107, 168-170).	Indirect[2]

1. Possibily by treating the viral infection; 2. Trough anti-inflammatory effect.

DISCUSSION

COVID-19 infection, like other infectious diseases, is associated with inflammation (17, 19, 22, 27). Growing evidence indicates the host immunologic reactions to COVID-19 is associated with hyperinflammatory responses such as cytokine storm, which play a major role in COVID-19 severity and death, and usually associated with poor disease prognosis (21, 23-25, 100). Higher levels of inflammatory cytokines such as IL-6, IL-10, and TNF-α are noted in patients with severe symptoms (23, 24, 26). Therapeutic consequences of altered cytokines expression have long been well acknowledged (171). Therefore, eradication of the virus with antiviral therapy is possibly not a sufficient strategy to reverse the side effects of the disease, mainly the damages caused by inflammation. Thus, during the disease, it is important to simultaneously fight the virus and manage the symptoms resulted from the inflammatory process. Indeed, as depicted in Table 2 all drugs used to treat COVID-19 patients have direct or indirect anti-inflammatory effects.

With regard to the effect of the renin-angiotensin system, it is important to point out that although the listed drugs may be void of direct effects on the, their anti-inflammatory effect indirectly influences the system (30, 43).

The data on the beneficial effects of the drugs used to treat COVID-19 patients are mainly unconvincing (60, 64). Many reports are only clinical observations that lack the inclusion of placebo or control arms. Thus, it is unclear whether the patient would have recuperated even without the use of those drugs.

In general, Inflammation is a fundamental and protective reaction of the body to infections and injuries. Acute inflammation is a beneficial function in a short time, which results in healing and could help eradicate infections. However, chronic inflammation is a prolonged and dysregulated process, which involves active inflammation and is associated with many pathophysiological conditions such as atherosclerosis, cancer, arthritis, and autoimmune diseases (28, 29). Inflammation is a complex condition with great inter- and intra-patient variability (172). As such, the severity of inflammation may play a role in therapeutic outcomes. In addition, anti-inflammatory properties of drugs are not always instantaneous, thus, the optimal effect may not appear in weeks and months. The exception being the most potent anti-inflammatory class of drugs, the corticosteroids that produce anti-inflammatory responses almost immediately. Indeed, in treating patients who are afflicted with arthritis, another inflammatory disease, initial and short-term therapy with corticosteroids is common while awaiting the optimal effects of other safer anti-inflammatory drugs. Interestingly, early data suggest a significant beneficial effect of corticosteroid therapy in COVID-19 patients (104-107, 173). Such a beneficial effect may not only be due to the strong anti-inflammatory effect of corticosteroids but also, the quick onset of the action of these drugs. COVID-19 infection is an invasive inflammatory affliction that needs intervention with quick therapeutic outcomes that are not expected from most anti-inflammatory drugs. Indeed, the optimal anti-inflammatory

effect of hydroxychloroquine is reported to take weeks (113, 114, 174), much longer than a quick multi-organ invasion of COVID-19.

The disease severity or the extent of inflammation may significantly influence the response to pharmacotherapy. This may not be a significant consideration when mere antiviral therapy is being used; but when attempting to combat inflammation associated with the viral infection, the disease severity can be of prime importance. Examples learned from other inflammatory conditions include the treatment of post-myocardial infarction patients whose survival rate depends significantly on the concentration of pro-inflammatory markers. Indeed, the higher the C-reactive protein concentration, the shorter will be the survival time (Figure 2) (175). It is also been reported that patients with active inflammation do not respond well to some important cardiovascular drugs (176-178). Inflammation downregulate proteins involved in the metabolism of many drugs including the blockers of calcium channel (179, 180), and the beta-adrenergic blocker antihypertension drugs (176). The downregulation causes high plasma concentrations of these medications. Interestingly, however, despite increased concentration, the efficacy of these drugs is reduced due to the downregulation of the receptors needed to exert effects. Controlling inflammation reverses these protein downregulations (177). The beneficial effects of drugs that interrupt angiotensin effects such as losartan (181) and valsartan (182) are not influenced by inflammation. Therefore, the influence of inflammation on response to cardiovascular drugs, and the choice of medication are important considerations in treating COVID-19 patients since the infection is associated with cardiovascular complications.

Currently, there is no specific pharmacological treatment for COVID-19 infection, thus, the therapy emphasizes the supportive care and management of the complications that are caused mainly by inflammation. In authors' opinion,

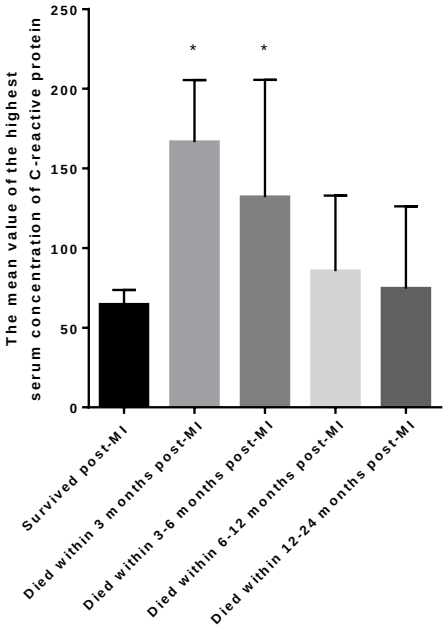

Figure 2. The effect of the extent of inflammation reflected as serum mean C-reactive protein concentration measure within 48 h post-myocardial infarction. Despite substantial variance, the first 6 months data were significantly different from the survived group. Adapted from reference 168. *= significant, $p < 0.05$.

treatment with anti-inflammatory drugs can be beneficial in COVID-19 patients with severe hyperinflammatory conditions. However, the efficacy of this treatment still needs well-planned clinical trials. There are several ongoing clinical trials on the treatment/management of COVID 19 (https://clinicaltrials.gov/ct2/who_table). In such trials, careful attention must be paid to the duration of the treatment, the onset of beneficial effects, and the severity of the disease, otherwise, the outcomes may still remain inconclusive. Additionally, it should be considered that the ongoing research efforts worldwide continuously provide more understanding of COVID-19 pathophisiology, which in turn provides us with more efficient treatment guidelines. This is a possibility that other drugs with no anti-inflammatory properties may

prove beneficial, although the pathophysiology may suggest otherwise.

CONCLUSION

COVID-19 severe clinical manifestation is most likely due to the host immunologic reactions. The inflammatory processes consequently damage several patient's organs and may result in severe illness and death. Controlling the inflammation quickly and long enough with appropriate anti-inflammatory drugs is the key to successfully manage the disease. In treating cardiovascular complications, the influence of inflammation must be considered.

CONFLICT OF INTEREST

Authots have no conflict of interest pertaining to the content of this article.

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