Cytokine storm and probable role of immunoregulatory drugs in COVID-19: a comprehensive review

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The coronavirus disease 2019 (COVID-19) is currently the most important global health problem. Due to its pandemic state and high mortality rate, it is critical to find useful interventions that reduce the mortality rate and boost patient survival. Since there is no specific antiviral treatment for the disease and given the growing amount of data about the role of the inflammatory response and cytokine storm in increased disease severity, we evaluated the mechanisms and possible positive effects of some specific anti-inflammatory drugs on the disease course of COVID-19 and examined some suggested treatments in the form of a scoping review article. It is important to select patients who may benefit from these treatments without inflicting any serious adverse effects. In our view, in approaching COVID-19 patients, we should consider the severity of the body's inflammatory response. Mild cases may not require additional anti-inflammatory treatment or at least should be treated with safer immunoregulatory drugs such as chloroquines, whereas in severe cases with an overactive immune response evidenced by high serum inflammatory marker levels (TNF, ESR, CRP, WBC count, LDH, ferritin) and severe lung involvement in chest images, stronger immunoregulatory drugs (targeted immunotherapy) such as TNF and kinase inhibitors may be considered as adjunctive treatments in combination with antiviral drugs. However, further precisely designed studies are needed to confirm the therapeutic effect and safety of each of these anti-inflammatory drugs in COVID-19 patients and to determine their optimal dose, route of administration, and possible side effects.

Keywords: coronavirus, COVID-19, immunomodulatory drugs, anti-inflammatory drugs, immuno-target therapy

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INTRODUCTION

Coronaviruses are RNA viruses belonging to the Coronaviridae family named according to the crown-like spikes on their surface. There are four main sub-groups of coronaviruses, namely alpha, beta, gamma, and delta. Although most human coronavirus infections are mild (e.g., the common cold), the severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are two betacoronaviruses that have caused severe diseases with high mortality rates in the past two decades [1, 2]. In December 2019, a new form of viral pneumonia was reported in Wuhan, which rapidly spread to other countries and became a pandemic. Laboratory investigations showed the cause of this viral pneumonia was a novel coronavirus named as

the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical spectrum of this infection appears to be wide, ranging from asymptomatic infection and mild respiratory disease to severe viral pneumonia, multiorgan failure and death [3-6].

As studies have shown, one of the main causes of death in these patients is lung involvement resulting from an overactive immune response and the onset of a cytokine cascade. Patients infected with SARS-CoV-2 have increased serum levels of proinflammatory cytokines such as IL1B, IFN-γ, IP10, MCP1, GCSF, and TNF alpha; these changes are more prominent among those requiring ICU admission, suggesting that it may be associated with pulmonary inflammation and extensive lung damage, as seen in the SARS and MERS infections [5-8].

Furthermore, histological examinations of the lungs of COVID-19 patients have shown bilateral diffuse alveolar damage with cellular fibromyxoid exudates together with desquamation of pneumocytes, hyaline membrane formation, interstitial mononuclear inflammatory infiltration dominated by lymphocytes, and multinucleated syncytial cells with enlarged, atypical pneumocytes. These findings greatly resemble those seen in the SARS and MERS coronavirus infections and are in favor of acute respiratory distress syndrome (ARDS) [9].

Chemotactic factors are essential to the defense of the body against viral infections through the recruitment of leukocytes to the involved organ. Any decrease or increase in the level of chemotactic factors may lead to a severely maladjusted immune response that may increase viral replication or inflict unwanted damage to body tissues. In the lung, this inflammatory response maladjustment may result in pulmonary tissue damage, functional impairment, and reduced lung capacity [10-12].

As yet, there is no specifically approved antiviral treatment for COVID-19, and the mortality rate of the patients is steadily increasing [13,14]. Since it is postulated that the cytokine storm may be associated with severe forms of the disease that lead to death, it seems that the use of selective anti-inflammatory drugs along with suggested antiviral therapies can be effective in controlling the side effects of immune system hyperactivity and reducing the severity of the disease in selected patients who fail to respond to routine treatments and face deterioration over time.

We searched almost all new and related articles about the immunopathology of COVID-19, possible inflammatory pathways in viral injuries to the lungs and other organs, and certain anti-inflammatory drugs that can affect these mechanisms. We used the Medline, Scopus, Google Scholar, and Web of Science databases for finding the articles of this comprehensive scoping review.

Although the immunological mechanisms through which coronaviruses induce tissue changes are not fully understood, the involvement of interleukin (IL) 1, 6, and 8, tumor necrosis factor alpha (TNFα), the JAK-STAT pathway, and interferons (IFNs) has been demonstrated in various studies. After the virus enters the body, antigen-presenting cells (APCs) are the first cells that present the pathogen-associated molecular patterns to T cells. Then, immune cells are activated and release inflammatory mediators, such as TNFα, IL-1, IL-6, IL-8, prostaglandins, and histamine. These mediators affect the vascular endothelium in the involved organ, leading to an increase in vascular permeability and dilation together with the recruitment of leukocytes (neutrophils, monocytes, macrophages, and lymphocytes) and the stimulation of the T-helper 1 pathway for cytotoxic activity and T-helper 2 pathway for antibody formation. These pulmonary microvascular changes are the first step in the development of ARDS and severe systemic inflammation-induced lung injury [11,12,15-17]. In the macaque model of age-dependent SARS-CoV pathogenesis, NF-kB induced genes, which are the master regulators of immune and inflammatory processes in response to both injury and infection and cause higher levels of IFNs, are more highly expressed in aged macaques compared to young adult macaques [18,19]. This may partly explain the higher mortality rate in the elderly compared to young patients and may also be the reason why the regulation of the immune response in these individuals can possibly reduce the disease severity and mortality.

There is a wide range of anti-inflammatory agents that suppress immune responses selectively or non-selectively. Corticosteroids comprise a group of common, non-selective immune suppressants that may be helpful in reducing inflammatory-induced tissue injuries but can also aggravate viral replication and spread. Therefore, medications that can selectively influence the

inflammatory process may be more appropriate in this context. Chloroquines, intravenous immunoglobulin (IVIG), interferons, selective interleukin inhibitors that cause IL-1 and IL-6 receptor blockade (anakinra and tocilizumab, respectively), TNF inhibitors, and JAK inhibitors are examples of targeted anti-inflammatory drugs. Herein, we theoretically discuss the possible mechanisms of some of these drugs in patients with COVID-19 and examine the related clinical evidence and existing controversies. It is important to note that none of these drugs have yet been approved for the treatment of patients with COVID-19, and their routine and safe use for these patients require further investigation.

1- Chloroquines. Chloroquine and hydroxychloroquine are antimalarial agents that act through the stabilization of lysosomes within injured cells and the inhibition of antigen presentation, cell-mediated immunity, and cytokine production (particularly pro-inflammatory factors such as TNF-a, IL-1b, IL-6 and IFN-gamma from human monocytes/macrophages), as well as exerting antithrombotic/antiplatelet effects. The protective effect attributed to antimalarials may stem from their anti-inflammatory properties [20]. They are also used in some rheumatologic or dermatologic inflammatory and autoimmune diseases due to their immunomodulatory effects. Furthermore, some studies have demonstrated the antiviral effects of these drugs in SARS coronavirus and influenza virus infections. However, the effect of these drugs on COVID-19 is still controversial; although positive results were initially reported in terms of boosting virus clearance and improving the clinical course [21-27], some recent studies have reported no effects and even side effects such as cardiac arrhythmias in patients with COVID-19 who have received these drugs, especially in combination with macrolides [28-31]. The exact antiviral mechanism of these drugs has not been defined but some possible mechanisms in treating COVID-19 have been proposed and shown in vitro. These mechanisms include the elevation of lysosomal pH and interference with the terminal glycosylation of ACE2, leading to the inhibition of the entrance and replication of the virus [32].

In some recent studies on COVID-19 patients, thromboembolic events have been highlighted as a mechanism of worsening condition and mortality. Due to the link between inflammation and hypercoagulation and given the destructive effect of a hyperactive immune response, these drugs may be theoretically useful in the treatment of COVID-19 patients as they offer both antiplatelet and anti-inflammatory effects [33,34]. Despite all the beneficial effects mentioned for these drugs, the definite effect as well as the safety of these drugs in the treatment of COVID-19 is yet to be fully understood and requires further investigations and clinical studies.

2- TNF alpha inhibitors. One potential target for immunotherapy is the tumor necrosis factor (TNF), a cytokine produced by monocytes, macrophages, and T lymphocytes. There are two widely distributed high-affinity receptors for TNF that promote either cell proliferation or cell death. This cytokine has multiple functions. It has diverse biological activities and plays critical roles in inflammation, in increasing MHC class I display on target cells, and in boosting Cytotoxic T lymphocyte (CTL) killing. A possible mechanism by which TNF may cause increased disease severity is the up-regulation of adhesion molecules on endothelial cells of vessels, leading to extravasation and recruitment of cells to normal and inflamed tissues (the lung in the case of COVID-19), and may play a role in early neutrophil and eosinophil recruitment, perhaps by boosting chemokine production. The decrease in unnecessary or destructive activation of inflammatory cells would effectively reduce the amount of damage to otherwise healthy areas of the lung. It seems that disease severity in many patients is caused by an exuberant immune response rather than viral replication. In this situation, TNF inhibition is clearly beneficial [35-38].

In a few studies, a beneficial effect of TNF depletion has been demonstrated in viral lung diseases such as the respiratory syncytial virus (RSV), influenza A virus, and the SARS-CoV, with no evidence that TNF depletion significantly compromised viral clearance or the production of virus-specific antibodies. In fact, TNF depletion was found to reduce pulmonary recruitment of inflammatory cells, cytokine production by T cells, and the severity of illness without preventing virus clearance. These broad beneficial effects suggest that TNF antagonists might be tested as treatments of human viral lung diseases [39,40]. The safety and definite roles of these drugs in the treatment of

patients with COVID-19 remain to be established. In some studies, the use of some agents in this group such as adalimumab and infliximab has been suggested, especially in the first few days of admission of patients with moderate disease to prevent disease progression [41]. Some studies have also proposed that these drugs do not play a role in the worsening of the clinical course and condition of COVID-19 patients [42,43]. Of this group of drugs, adalimumab is the only TNF-α inhibitor that has been registered in two clinical trials in China for evaluation in COVID-19 patients (ChiCTR2000030580; ChiCTR2000030089).

3- Cellular kinase inhibitors. Cellular kinase inhibitors such as JAK, AAK1, and GAK inhibitors comprise another group of targeted immunotherapy agents that block cytokine signaling [44]. Given that JAK inhibitors decrease cytokine expression and interfere with cytokine signaling pathways including IL-6 and IFN, they may be useful in the limitation of the cytokine storm and excessive inflammatory response seen in severe cases of COVID-19. Furthermore, it is proposed that some of these drugs like baricitinib may also reduce viral entry via the inhibition of AAK1 in addition to their potential anti-inflammatory effects in COVID-19 patients [45-50]. Due to the lower probability of drug interactions in baricitinib compared to other drugs of this family, this drug is a candidate in combination with antiviral drugs in the treatment of COVID-19 patients [43,51]. The effect of the mentioned drugs in the treatment of other viral diseases (dengue fever) has also been shown [52]. Despite these positive effects, the inhibition of IFN, which plays an important role in body defense against viruses, may be harmful. This is particularly significant in the early stage of COVID-19 because, in this phase, it has been proposed that SARS-COV-2 reduces IFN expression and further IFN inhibition with these drugs may increase viral replication, meaning that the effectiveness and benefits of these drugs in COVID-19 patients are controversial and require well-designed investigations [12,43,51]. To our knowledge, two clinical trials are ongoing to evaluate the efficacy and safety of two kinds of JAK inhibitors in COVID-19, namely Jakotinib hydrochloride tablets and ruxolitinib (ChiCTR2000030170 and ChiCTR2000029580, respectively). There are some multipotential immunomodulator drugs that have been proposed as adjuvant therapies for the treatment of COVID-19 like pentoxifillyne [53] and N-acetyl cysteine [54-56], but more clinical trials are needed on logically effective drugs with acceptable safety profiles.

CONCLUSION

These days, the COVID-19 pandemic has become the world's biggest crisis. Since no definitive treatment for the disease has been found so far, and considering the potential role of immune system hyperactivity in exacerbating the symptoms, some anti-inflammatory drugs may be helpful as adjunctive treatments for reducing the severity of the disease in specific cases and in the absence of possible contraindications. Such cases include patients with a severe course of disease who don't respond to routine treatments and are prone to death. They may reduce tissue injuries that result from overactive immune responses. However, it is important to know the adverse effects and risks of the use of such drugs, and case selection for anti-inflammatory treatment may be very critical. The hypothesis presented should be further evaluated in the form of case report studies and/or clinical trials.

In our view, in approaching COVID-19 patients, we must consider the severity of the body's inflammatory response. Mild cases may not require additional anti-inflammatory treatment or at least should be treated with safer immunoregulatory drugs such as chloroquines, whereas in severe cases with an overactive immune response evidenced by high serum inflammatory marker levels (TNF, ESR, CRP, WBC count, LDH, ferritin) and severe lung involvement in chest images, stronger immunoregulatory drugs (targeted immunotherapy) such as TNF and kinase inhibitors may be considered as adjunctive treatments in combination with antiviral drugs. However, further precisely designed studies are needed to confirm the therapeutic effect and safety of each of these anti-inflammatory drugs in COVID-19 patients and to determine their optimal dose, route of administration, and possible side effects.

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