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Review Article

Cytokine storm in COVID-19: Potential therapeutics for immunomodulation

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The outbreak of new coronavirus disease-2019 or COVID-19 infection has become a global health emergency at the beginning of this year. Currently, no specific vaccines and therapeutic medications are available to treat this disease. Even though several vaccine candidates are under investigation, it will take some time to make them available for the mass population. Hyperinflammation due to excessive cytokine release in COVID-19 infected patients with other inflammatory diseases makes lethal effects, including multiorgan failure and even death. The increasing gain of insight about the pathophysiology of this novel coronavirus enables experts to consider some commonly available anti-inflammatory drugs as potential immunomodulatory candidates for the cytokine release syndrome (CRS) treatment in COVID-19 infection. This review was conducted to discuss all the possible signalling pathways involved in COVID-19 related hyperinflammation. It also emphasized on the efficacy of both synthetic and natural therapeutic drugs for immunomodulation in the COVID-19 related CRS treatment.

Background

Coronavirus disease-2019 (COVID-19) is a respiratory syndrome disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is a new strain of the Coronaviridae family of viruses.[1] At the end of last year (December 2019), this new type of respiratory syndrome disease was recognized to have erupted in Wuhan, China.[2] In March 2020, the World Health Organization (WHO) recognized this disease as a global pandemic.[3] Despite the unprecedented social distancing and other restrictions, the situation is still out of control, resulting in unexpected global economic and health impacts. According to the recent case studies, COVID-19 manifested by severe pneumonia with alveolar damage, which leads to severe acute respiratory distress syndrome (ARDS) (up to 20% of COVID-19 cases) and in worse cases even death.[4] In such cases, this novel virus elicits an uncontrolled release of proinflammatory cytokines, leading to cytokine release syndrome (CRS) or 'cytokine storm'.[4,5] Activation of CRS worsens the ARDS and can lead to multiple organ dysfunction.[6,7] Evidence suggests that SARS-CoV-2 infected patients who are already suffering from immune-rheumatological and other inflammatory diseases like rheumatoid arthritis (RA) are more fragile to CRS-induced ARDS.[8-10] It is because the cytokine storm or CRS is common in both COVID-19 patients and rheumatological patients.[8,11] Although no specific therapeutics or vaccine is currently available to halt the epidemic, CRS suppressing therapeutics like tocilizumab has been in clinical trials to treat COVID-19.[12,13] Despite these clinical trials, the best strategy to manage COVID-19 in rheumatological patients during this emergency period is still unclear. The principle goal of this review is to provide an overview of the hyperinflammatory response mechanism that causes CRS in COVID-19 patients, with a specific focus on the available options of anti-inflammatory therapeutics for immunomodulation in the context of this health emergency.

Hyperinflammatory response in COVID-19 infection

Cytokines are a broad group of small proteins that are released by cells to control cell functionalities like proliferation and differentiation.[14] Despite these functions, another significant role of cytokines is to regulate immune and inflammatory responses.[14] In COVID-19 infection, the uncoated viral RNA genome is released into the cytoplasm to allow two polyproteins to translate, followed by transcription of the sub-genomic RNAs and viral genome replication.[15] This results in the progression of CRS-induced ARDS due to the upregulation of proinflammatory cytokines. This massive cytokine release is analogous to secondary hemophagocytic lymphohistiocytosis (sHLH), which is characterized by persistent activation of natural killer (NK) cells and cytotoxic T cells.[16-18] In most severe

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COVID-19 infections, it has been reported that cytokine profiles confirm the increased levels of interleukin-1β (IL-1β), IL-2, IL-6, IL-8, tumour necrosis factor-α or TNF-α and some chemokines.[19,20] These elevated levels of cytokines and chemokines confirm the sHLH syndrome in COVID-19 patients. Major clinical manifestations of sHLH include unremitting fever, enlarged liver, liver dysfunction, cytopenias, neurologic dysfunction, and multiorgan failure.[21,22] It is considered that the host response to infection can trigger clinical and laboratory manifestations of CRS and sHLH.[23] Recent literature indicates that SARS-CoV-2 infection triggers CRS and sHLH in critical patients.[4, 24-26]

In COVID-19 infection, SARS-CoV-2 envelope spike glycoprotein uses transmembrane serine protease-2 (TMPRSS2) and angiotensin converting enzyme II (ACE2) as the cell entry receptors.[27] Host-virus interaction via these cell surface receptors induces the hyper-activation of the nuclear factor-κB (NF-κB), mostly in nonimmune cells, including lung epithelial cells, which in turn activate the production of more cytokines and chemokines.[28,29] Excessive production of cytokines triggers the CRS-induced ARDS in infected patients. SARS-CoV-2 itself also activates NF-κB via pattern recognition receptors (PRRs).[30] SARS-CoV-2 mostly occupies ACE2 molecules on the cell surface.[31] This membrane protein is considered as an inactivator of angiotensin 2 (AngII).[32] Due to the reduction of ACE2 on cells, AngII increases in the serum.[33] AngII acts both as a vasoconstrictor and proinflammatory cytokine via angiotensin receptor type 1 (AT1R).[34] The AngII-AT1R complex activates NF-κB along with disintegrin and metalloprotease 17 (ADAM17). This results in the generation of the mature forms of TNF-α, epidermal growth factor receptor (EGFR), and two NF-κB stimulators.[35] ADAM17 induces the conversion of membrane form of IL-6Rα to the soluble form (sIL-6Rα). The sIL-6Rα-IL-6 complex drives the gp130-mediated activation of transcription factor STAT3 in different IL-6Rα-negative nonimmune cells like endothelial cells, fibroblasts, and epithelial cells.[36,37] This STAT3 is crucial for the enhanced activation of NF-κB machinery. During inflammation, the main stimulator of STAT3 is IL-6.[38] Therefore, SARS-CoV-2 infection triggers the activation of both NF-κB and STAT3 in the respiratory system. It is postulated that the IL-6 amplifier (IL-6 Amp) induces the release of a variety of proinflammatory cytokines, e.g., IL-6 via hyperactivation of NF-κB by STAT3.[30] Therefore, IL-6 Amp might correspond to the CRS-induced ARDS in COVID-19 patients, a disorder induced by cytokine storms.

Possible immunomodulatory therapeutics to mitigate CRS in COVID-19 infection

Although upstream prevention strategies like vaccination are ideal for addressing the current clinical need, vaccines and approved therapeutic drugs for the SARS-CoV-2 infection treatment are still lacking.[39,40] Based on the previous epidemic history associated with SARS-CoV and middle east respiratory syndrome coronavirus (MERS-CoV), similar drugs (ribavirin, remdesivir, and lopinavir-ritonavir) have been considered even for COVID-19 treatment despite their controversial results.[41-44] With the rapid increase of critically ill patients, it is urgent to identify specific molecular targets in the key pathogenesis pathways that can be manipulated. The use of these therapeutic targets for immunomodulation can mitigate the hyperinflammatory states or CRS in COVID-19 patients (Table 1). However, many anti-inflammatory therapeutic drugs commonly used in the rheumatological disease treatments have been proposed recently as possible immunomodulatory drugs for COVID-19 treatment.[8,9]

Renin-angiotensin-aldosterone system (RAAS) inhibitors

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are two primary renin-angiotensin-aldosterone system (RAAS) inhibitors.[45] These two RAAS inhibitors are highly recommended therapeutics for patients with cardiovascular diseases and patients with diabetes and renal insufficiency.[46] SARS-CoV-2 gains entry to the lower respiratory tract of infected patients by using the membrane-bound ACE2 protein receptor (Figure 1). Therefore, it is hypothesized that the ACEIs and ARBs treatment in COVID-19 patients might reduce the inflammation and would have potential benefits in the treatment of lung injury caused by COVID-19.[47,48] Nevertheless, in a recent descriptive study of 1099 patients with COVID-19 infections treated

Table 1. Clinical trials list of therapeutic drug candidates for COVID-19 treatment

Drug/Compound	Target	Clinical Trials
Baricitinib	JAK inhibitor	NCT04320277 (Phase II & III)
Tocilizumab	IL-6 inhibitor	NCT04335071 (Phase III)
Dexamethasone	Corticosteroid	NCT04381936 (Phase II & III)
Anakinra	IL-1 inhibitor	NCT04324021 (Phase II)
ECMO	Extracorporeal support therapy	NCT04385771 (Phase: Not Applicable)
IFN-β-1B	IFN protein	NCT04276688 (Phase II)
IFN-γ	IFN protein	NCT04344600 (Phase II), NCT04354259 (Phase II), NCT04388709 (Phase II), and NCT04343976 (Phase II)

JAK, Janus Kinase; IL, Interleukin, IFN, Interferon, ECMO, Extracorporeal membrane oxygenation.

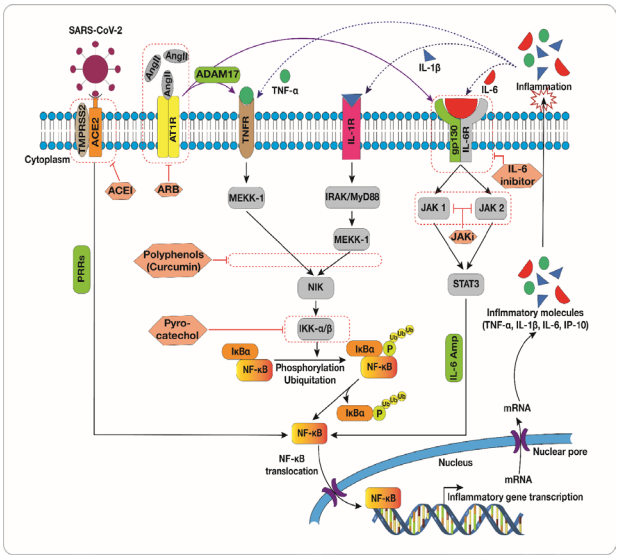

Figure 1. Signalling pathways involved in the cytokine release syndrome (CRS) during SARS-CoV-2 infection and potential immunomodulatory therapeutic targets. In normal condition, ACE2 receptor inhibits AngII expression. SARS-CoV-2 interacts with ACE2 and TMPRSS2 receptors via spike protein, which in return activates AT1R receptor by uninhibited AngII. This novel virus itself activates NF-**κ**B via PRRs. AT1R activation induces activation of TNF-**α** and IL-6 via ADAM17 which in turn induce activation of IL-6 Amp, a mechanism for the hyperactivation of NF-**κ**B by STAT3. Hyperactivated NF-**κ**B triggers the excessive secretion of inflammatory molecules resulting in CRS. ACEIs, ARBs, JAKi, IL-6 inhibitors, and plant polyphenols can limit hyperinflammation by interacting and inhibiting these signalling cascades within the inflammatory system.

in China between 11 December 2019 and 29 January 2020, Guan et al. reported that more severe disease outcomes were observed in patients with diabetes, hypertension, chronic renal disease, and coronary artery disease.[49] All these patients were treated with ACEIs or ARBs, which indicated that the treatment with these RAAS inhibitors acted as a risk factor for more severe disease outcomes. Some other studies reported that the expression of ACE2 might be increased in patients with diabetes mellitus who were treated with ACEIs and ARBs.[50,51] There are conflicting data on the effects of these two RAAS inhibitors on ACE2 expression. A recent retrospective study of 1128 COVID-19 patients in hospitals suggested that patients who received ACEIs or ARBs had improved outcomes compared to those who did not receive those medications.[52] Some data suggest that ACE2 decreases after COVID-19 infection, and it is hypothesized that the unregulated AngII is the primary culprit behind the CRS and tissue damage.[45] Moreover, it is also considered that the physiologic relevance of ACE2 may be tissue-specific, therefore, data on the effects of RAAS inhibition on lung ACE2 are missing.[45] Several clinical trials currently assess the efficacy of both recombinant ACE2 and losartan (a commercial ARB) as potential therapeutic candidates for the treatment of CRS-induced ARDS in COVID-19 patients.[53-55] Hopefully, the outcomes of these trials will provide us with some answers to all these crucial inquiries regarding the efficacy of RAAS inhibitors.

Janus kinase (JAK) inhibitors

Another way to restrain the excessive level of cytokine signalling or cytokine storm is the use of Janus kinase inhibitors (JAKi).[56,57] Most JAK inhibitors are specifically effective at JAK1 and JAK2 inhibition (Figure 1), and therefore, inhibit multiple cytokines including IL-6, IL-2, interferon (IFN)-α/β and IFN-γ signalling cascade.[58–60] Baricitinib is a type of JAKi which might impair early stages of the SARS-CoV-2 virus spread via endocytosis and inhibit the several cytokines signalling relevant to the pathogenesis of viral pneumonia.[57] These results suggest that JAK inhibitors may be effective in reducing the clinical symptoms via modulating inflammatory cytokines in the different organs like the lungs, kidneys, and heart that are affected by the disease complication. Several clinical trials were conducted to examine the use of baricitinib and other JAK inhibitors like ruxolitinib and tofacitinib in COVID-19 patients (NCT04320277).[56,57,61] Results indicate that baricitinib-treated patients achieved better clinical improvements compared to others. Furthermore, a recent study suggests that most JAK inhibitors have been associated with induced risk for some complications, including thrombosis and viral reactivation.[61,62] Moreover, there are some contradictory findings over monotherapy or combination therapy of baricitinib and methotrexate, a folate antagonist that broadly used for rheumatoid arthritis treatment.[63,64] Therefore, further understanding of the JAK inhibitors' role is required to implement this biologic agent as a potential therapeutic to interfere with the cytokine cascade driving CRS in COVID-19 patients.

IL-6 inhibitors

IL-6 is a type of cytokine that participates in a wide range of immune and inflammatory events. IL-6 binds to IL-6R and glycoprotein-130 (gp130) to form a hexameric complex.[65] In such a hexameric complex, both membrane-bound IL-6R and soluble IL-6R are associated with the cis- and trans-signalling pathways, respectively.[66] In the context of infection, IL-6 can have both local inflammatory and other systemic effects. As IL-6 plays a vital role in the immune and inflammatory dysfunctions, pharmacological anti-IL-6 or anti-IL-6R therapy could prevent IL-6 from binding to IL-6R by either targeting cytokine itself or the receptor.[67] Therefore, IL-6 inhibitor-based therapy could relieve various hyperinflammatory symptoms like fever, fatigue, pain, and others.[67,68] Since the early 1990s, IL-6 inhibitors have been applied to treat rheumatoid arthritis that primarily affects the joints.[69] In 2017, FDA approved tocilizumab, an IL-6 inhibitor for the treatment of life-threatening chimeric antigen receptor (CAR) T cell-induced CRS in both adults and children.[70] This approval was based on a retrospective

study of data from clinical trials showing the efficacy of tocilizumab treatment in patients who developed CRS after CART cell therapy.[71] It is hypothesized that IL-6 inhibitor could be an option to treat hyperinflammation (due to elevated concentrations of IL-6) or CRS-induced ARDS in COVID-19 pneumonia patients.[4,5] A phase III trial (NCT04335071) of IL-6 inhibitor treatment was approved by the Food and Drug Administration (FDA) in March 2020 to assess the efficacy of tocilizumab for severe COVID-19 patients.[67] It is expected that the findings from current clinical trial will expand the application of IL-6 inhibitor-based therapy for the treatment of CRS or hyperinflammation in COVID-19 patients.

NF-κB inhibitors

In COVID-19 infection, phosphorylation of NF-κB inhibitor-α (IkB-α) and its proteasomal degradation help to dissociate NF-κB complex and trigger the translocation of NF-κB into the nucleus. NF-κB then mediates the induction of several pro-inflammatory cytokines like TNF-α, IL-1, IL-2, IL-6, and some chemokines.[72–74] Therefore, such events induce the further recruitment of inflammatory immune cells, which exacerbate and perpetuate the inflammatory process, i.e., hyperinflammation or CRS in SARS-CoV-2 infected patients.

Plant metabolites as NF-κB inhibitors

Many dietary plants such as fruits, vegetables, and whole grains are rich in polyphenolic compounds, including curcumin, apigenin, flavonoids, quercetin, and (E)-resveratrol.[75-77] These plant polyphenols have been shown to have anti-inflammatory activities in *in vitro* studies.[78–81] In general, polyphenols have been shown to intervene at two specific sites in the NF-κB pathway. In one way, some polyphenols inhibit phosphorylation or ubiquitination of kinases and thereby halt the subsequent breakdown of IκB.[77] In return, this event prevents the translocation of NF-κB into the nucleus and, therefore, inhibits the transcription of pro-inflammatory cytokines. Alternatively, another proposed mode of action of anti-inflammatory polyphenols is the inhibition of the interaction of NF-κB subunits with target DNA.[77] Both mechanisms ultimately trigger the inhibition of various NF-κB regulated pro-inflammatory cytokines and chemokines expression.

Curcumin is a type of polyphenol that can be found in turmeric.[82] Curcumin is a polyphenol that regulates cytokine-induced NF-κB activation. The inhibition of cytokine-mediated IκBα phosphorylation and degradation by curcumin causes the blockade of NF-κB signalling via decreasing IκB kinase complex (IKK) activity.[83-85] Direct interferences with NF-κB-inducing kinase (NIK) or IKK activity do not mediate the inhibitory function of curcumin.[85] It means that the curcumin functions at a level upstream of NIK activation. Results from previous studies indicate that curcumin potently inhibits cytokine-mediated NF-κB signalling via blocking the signal towards the IKK complex by intervening a signal upstream from NIK.[83-85] Therefore, curcumin-based therapeutics could be a potential alternative in inhibiting NF-κB activation and proinflammatory gene expression.

Natural flavonoids have been shown to interact with intracellular signalling pathways and, therefore, control the inflammatory gene expression.[86,87] The most prominent mode of action of flavonoids is to diminish the NF-κB activity by inhibiting upstream events such as reducing the IKK phosphorylation.[88,89] It leads to the less degradation of IκB or attenuation of the DNA-binding capacity of NF-κB.[88] Therefore, flavonoids exert an anti-inflammatory effect by inhibiting the proinflammatory cytokine release. Apigenin is a natural polyphenolic flavonoid that can be found in parsley, celery, chamomile plant, and grapefruit.[90] Apigenin has been shown to attenuate inflammatory response via suppression of the NF-κB signalling.[90] This results in reduced excessive secretion of proinflammatory cytokines IL-6 and TNF-α.

Pyrocatechol is another plant metabolite that can be found in roasted coffee.[91] Roasting of the coffee beans triggers the formation of pyrocatechol from chlorogenic acid, an element found in coffee beans. This plant metabolite exhibits anti-inflammatory activity via inhibition of NF-κB signalling.[91] Therefore, it suppresses the mRNA expression of different proinflammatory cytokines, including most prominent IL-6.

These are the primary natural plant metabolites that can be potential immunomodulatory therapeutic candidates for the CRS treatment in COVID-19 patients.

Other potential therapeutic options

Corticosteroids are a class of steroid hormones that could be used to halt the cytokine storm by regulating the transcription of anti-inflammatory genes.[92] Although corticosteroids have been recommended widely for anti-inflammatory treatment like influenza, but still the effectiveness of corticosteroid treatment has been a matter of debate.[93] Dexamethasone is a type of corticosteroid that acts on the immune system to dampen the massive inflammation in the lungs and heart of the severely ill ARDS patients. Recently in UK, the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, the largest COVID-19 drug trial, has been conducted to test the effectiveness of dexamethasone.[94] In that trial, around 2000 patients were given dexamethasone and the results were compared with more than 4000 patients who did not receive it. The trial results came quite promising as dexamethasone decreased the death risk of mechanically ventilated patients from 40 to 28 percent. The death risk of patients who required oxygen dropped down from 25 to 20 percent.[94] Such promising new research suggests that using commonly available steroids to treat COVID-19 patients with ARDS may help to reduce COVID-19 related mortality.

Another potential therapeutic that could be considered an immunomodulatory drug is etoposide, which is used to suppress excessive cytokine release via depleting monocytes in HLH.[95] A significant increase of $CD14^{+}CD16^{+}$ monocytes and a predominance of inflammatory monocyte-derived macrophages were detected in COVID-19 patients with severe illness.[96] The hyperactivation of monocytes/macrophages accelerates the inflammation and promotes fibrosis generation.[96] Thereby, it is recommended that etoposide could be a potential therapeutic option to suppress the hyperactivation of these monocytes/macrophages to inhibit the excessive inflammatory response and to alleviate pulmonary fibrosis.[97]

Anakinra is a recombinant interleukin-1 or IL-1 receptor antagonist commonly used to treat autoinflammatory disorders like systemic-onset juvenile idiopathic arthritis, familial Mediterranean fever, and adult-onset Still's disease.[98] This IL-1 receptor antagonist blocks pro-inflammatory cytokines IL-1α and IL-1β activity to reduce hyperinflammatory symptoms in patients.[99] At the San Raffaele Hospital in Italy, recently (from March 10 to March 27, 2020) 29 patients received high-dose of intravenous anakinra with non-invasive ventilation and standard treatment, 16 patients received only non-invasive ventilation and standard treatment, and a further 7 patients received low-dose subcutaneous anakinra with non-invasive ventilation and standard treatment.[99] This retrospective cohort study found that treatment with high-dose anakinra with non-invasive ventilation outside of the intensive care unit (ICU) in patients with COVID-19 and ARDS was safe. Treatment with a high-dose of anakinra was also associated with serum C-reactive protein reductions and gradual respiratory function improvements in 72% of patients. A similar study was conducted in France to check the efficacy of anakinra in severely ill patients.[100] That study also revealed that all of the patients treated with anakinra clinically improved (no death reports) with significant oxygen requirements reduction. These studies indicated that early blockade of the IL-1 receptor could be an option to treat acute hyperinflammatory respiratory failure in COVID-19 patients. Despite the success in these reports, some limitations like the low number of patients and uncontrolled nature of the study hinder its wide application for the treatment of COVID-19.[99,100] A phase-II clinical trial of intravenous anakinra in COVID-19 treatment is ongoing in Italy (NCT04324021).[99]

Extracorporeal support therapies like extracorporeal membrane oxygenation (ECMO) is another possible management strategy in critically ill patients who have refractory hypoxemic respiratory or cardiac failure.[101] ECMO is a form of modified cardiopulmonary bypass that provides respiratory support or circulatory support adding oxygen, and removing carbon dioxide. Therefore, blood is returned to the patient.[102] A randomized, controlled, open-label intervention, multi-centre clinical trial (CYCOV-II; NCT04385771) comparing cytokine adsorption in ECMO treatment for COVID-19 patients is ongoing to investigate the role of cytokine adsorption in severely affected COVID-19 patients requiring ECMO support.[103] The treatment of COVID-19 infected patients is particularly challenging from a medical perspective and requires a considerable amount of human and financial resources.[103,104] Besides, the coagulation function and blood gas of the patients are required to be monitored regularly during ECMO treatment to decide the time of ECMO use.

Type 1 interferons (IFN-1) are a group of cytokines with a broad antiviral activity *in vitro*.[105] Because of their antiviral activity, recombinant IFN-1 proteins (both IFN-α and IFN-β) are currently under investigation to check their efficacy in treating COVID-19 either as a single agent or in combination with other antiviral agents.[106] Some recent studies have reported a favourable response, and reduced mortality to early IFN-α and IFN-β use (for example, NCT04276688).[107] There are 18 more studies currently under investigation to test the clinical efficacies of IFN-α or IFN-β. IFN-III or IFN-γ is an alternative to IFN-1 due to their antiviral activities without any inflammatory effects. Currently, four studies are ongoing to investigate the clinical efficacies of recombinant IFN- (NCT04344600, NCT04354259, NCT04388709, and NCT04343976) (Table 1).[106] It is notable that some conflicting results have been reported for the strength of IFN responses in severely ill COVID-19 infected patients.[105,106] Therefore, more precise information is required from the currently ongoing clinical trials for the appropriate therapeutic use of IFN-based COVID-19 treatment.

Importance of potential immunomodulatory therapeutic targets

Currently, potential vaccines and targeted therapeutics for the treatment of COVID-19 related complications are under clinical trials, and it will take some time to commercialize the effective one for the management of the current epidemic. The only option for the COVID-19 management right now is supportive, but this is not sufficient to mitigate the complications in severely ill and elderly COVID-19 infected patients. Therefore, it is essential to identify and select an effective therapeutic strategy to treat COVID-19 infection by testing the efficacy of existing anti-viral therapeutics used for other viral infections. Recently, human monoclonal antibodies attaching to the spike protein of SARS-CoV-2 to neutralize the virus interaction with the host cells also showed promising results.[39] Besides, many drugs are available for the treatment of inflammatory diseases like arthritis and cardiovascular diseases. Patients with these diseases are more prone to have CRS-induced ARDS in COVID-19 infection, and thereby, these anti-inflammatory therapeutics could be an alternative therapy for CRS treatment in COVID-19 patients. Interestingly, almost all

Table 2. Potential therapeutic candidates for immunomodulation in COVID-19 infection

Therapeutic target	Commercial Name	Mode of action	Efficacy in COVID-19		Reference
			Pros	Cons	
RAAS inhibitors	Losartan (a commercial ARB) ACEIs	Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) inhibit ACE2 protein expression	Reduce inflammation; potential benefits in the treatment of COVID-19 related lung injury	Acts as a risk factor for more severe disease outcomes	45, 47, 48, 50, 51
JAK inhibitors	Baricitinib Ruxolitinib Tofacitinib	JAK1 and JAK2 inhibition to modulate inflammatory cytokines	Effective in reducing clinical symptoms caused by COVID-19 infection	Induce risk for some complications including thrombosis and viral reactivation	56, 61, 62
IL-6 inhibitors	Tocilizumab Siltuximab	Anti-inflammatory; Prevent IL-6 from binding to IL-6R	Reduce hyperinflammatory symptoms like fever, pain, etc.	Potential hazard to induce other infectious diseases	67, 68
NF-κB inhibitors	Curcumin Apigenin Pyrocatechol	Prevent translocation of NF-κB into the nucleus and inhibit transcription of pro-inflammatory cytokines	Exerts anti-inflammatory effect by inhibiting proinflammatory cytokine release	No known side effect in COVID-19	83-85, 90, 91
Corticosteroids	Dexamethasone	Regulate transcription of anti-inflammatory genes	Dampen the hyperinflammation in lungs and heart	Need more clinical outcomes	92, 94
Etoposide	Etopophos	Suppress the hyperactivation of monocytes/macrophages	Inhibit hyperinflammatory response and alleviate pulmonary fibrosis	Need more clinical outcomes	96, 97
IL-1 inhibitors	Anakinra	IL-1 receptor antagonist blocks proinflammatory cytokines IL-1α and IL-1β activity	Significant reduction in oxygen requirements in critically ill patients	Potential risks to induce other infectious diseases	99, 100
IFN proteins	Recombinant IFN-α/β/γ	Induce anti-viral activity	Significant reduction of complications caused by COVID-19 infection	More precise information required for proper therapeutic use	105, 106

RAAS, Renin-Angiotensin-Aldosterone System; COVID-19, Coronavirus disease-2019; ACE2, Angiotensin converting enzyme II; JAK, Janus Kinase; IL-6, Interleukin-6; IL-1, Interleukin-1; NF-κB, Nuclear Factor-κB; IF

the anti-inflammatory drugs work by regulating biological targets (e.g., ACEIs, IL-6 inhibitors, JAK inhibitors, NF-κB inhibitors, IL-1 inhibitors, corticosteroids, IFN and others) within the inflammatory systems in the body (Table 2). Over the decades, a wide range of therapeutic options as immunomodulatory drugs (e.g., tocilizumab, losartan, anakinra, siltuximab, dexamethasone, and others) have been practiced for hyperinflammation treatment. Plant-based natural anti-inflammatory compounds (e.g., polyphenols and catechol) could also be another potential treatment option in combination therapies with other medications to control CRS complications in critically ill COVID-19 patients.

Concluding Remarks and Future Direction

In conclusion, substantial clinical and laboratory evidence suggests that patients with chronic inflammatory diseases are more prone to COVID-19 severity like severe pneumonia and CRS-induced ARDS as well as different end-organ damage. Experts proposed a wide range of anti-viral and anti-inflammatory drugs as therapeutic targets due to the growing knowledge in the pathophysiology of the infection. Based on the clinical evidence, the use of ACEIs and ARBs should not be considered as standard therapy for high-risk COVID-19 patients. It is recommended that JAK inhibitors could be a potential approach to reduce the clinical symptoms in the COVID-19 infection. Despite their efficacy, high cost and certain adverse effects may limit their application. Tocilizumab is an IL-6 inhibitor that has been suggested for the CRS-induced ARDS treatment in COVID-19 patients. Although IL-6 and other IL-1 inhibitors are highly effective in controlling cytokine storm in rheumatic diseases, they have potential hazards to induce other infectious diseases. Despite the promising result of dexamethasone, it is important to determine

Study Highlights

What is current knowledge?

- COVID-19 infected patients with other inflammatory diseases are more prone to cytokine storm induced acute respiratory distress syndrome (ARDS)
- No specific vaccine or therapeutic medications are currently available to treat COVID-19

What is new here?

- All the possible signalling pathways involved in the COVID-19 related hyperinflammation were emphasized
- The efficacy of both synthetic and natural anti-inflammatory drug targets for immunomodulation in COVID-19 treatment were broadly discussed.

whether the effectiveness of such corticosteroids differ between ARDS phenotypes or not. Therefore, we need to be very cautious about using these agents and more clinical data that improve survival are required for their approval. Moreover, using these agents for the COVID-19 treatment remains highly controversial and requires further studies to clarify their efficacy in more severe cases of COVID-19 patients. Due to the anti-inflammatory potential of natural plant metabolites, it is highly recommended to consider the use of these compounds to form potential nutraceutical supplements, which may play a vital role in COVID-19 management. Based on the above circumstances, it is hardly deducible to conclude the efficacy of all the potential therapeutic targets. However, controlled clinical trials with meaningful outcomes are crucial to assess the therapeutic effects of these immunomodulatory targets for the CRS complications in COVID-19 patients.

Conflict of Interest

No conflict of interest is reported.

Ethic approval

Not applicable.

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