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Review article

Tackling the cytokine storm in COVID-19, challenges and hopes

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ABSTRACT

The outbreak of Coronavirus disease 2019 (COVID-19) is the current world health concern, presenting a public health dilemma with ascending morbidity and mortality rates exceeding any previous viral spread, without a standard effective treatment yet. SARS-CoV-2 infection is distinguished with multiple epidemiological and pathological features, one of them being the elevated levels of cytokine release, which in turn trigger an aberrant uncontrolled response known as "cytokine storm". This phenomenon contributes to severe acute respiratory distress syndrome (ARDS), leading to pneumonia and respiratory failure, which is considered a major contributor to COVID-19-associated fatality rates. Taking into account that the vast majority of the COVID-19 cases are aggravated by the respiratory and multiorgan failure triggered by the sustained release of cytokines, implementing therapeutics that alleviate or diminish the upregulated inflammatory response would provide a therapeutic advantage to COVID-19 patients. Indeed, dexamethasone, a widely available and inexpensive corticosteroid with anti-inflammatory effects, has shown a great promise in reducing mortality rates in COVID-19 patients. In this review, we have critically compared the clinical impact of several potential therapeutic agents that could block or interfere with the cytokine storm, such as IL-1 inhibitors, IL-6 inhibitors, mast cell targeting agents, and corticosteroids. This work focused on highlighting and contrasting the current success and limitations towards the involvement of these agents in future treatment protocols.

1. Introduction

Coronavirus disease 2019 (COVID-19) is the current world health concern that has been threatening the medical community since it was first reported in Wuhan, China on December 31, 2019 [1]. The outbreak started with 27 pneumonia cases reporting symptoms of fever, dyspnea, and lung damage [1]. Later on, the tests identified and labeled the causative agent of this infection as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the disease it caused was named by the World Health Organization (WHO) as COVID-19 [2]. While the wide majority of cases get resolved with minimal symptoms, some patients display fatal complications, such as septic shock, pulmonary edema, and acute respiratory distress syndrome (ARDS) [3]. SARS-CoV-2 is a single-stranded positive RNA, β-coronavirus belonging to the family of *Coronaviridae*. This family encompasses other viruses that bear sequence similarity to SARS-CoV-2, such as severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV [4]. SARS and MERS were the only two viral species from the coronavirus family that presented serious public health threats. In fact, SARS accounted for more than 8000 human infections and 774 deaths in 37 countries, as recorded during the period November 2002–August 2003 [5]. On the other hand, in 2012, MERS infection resulted in 2494 positive cases and 858 mortality cases [6]. The latest reports regarding COVID-19 revealed that the total cases as of May 16, 2020 are 4.56 million infections and 300,441 deaths worldwide [7]. Both SARS-CoV and SARS-CoV-2 gain cellular entry through the binding of their spike proteins to the receptor-binding domain (RBD) of the angiotensin-converting enzyme-2 receptor (ACE-2) [8]. However, the pandemic pattern of COVID-19 can be attributed to the higher binding affinity between SARS-CoV-2 and ACE-2 [9]. To date, the morbidity and mortality rates of COVID-19 are ascending with no curative therapeutic approach against the virus yet. The major

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contributor to COVID-19 associated fatality rates is the respiratory complications, as the lungs appear to be the most sensitive organ for this virus [10]. The reason for this sensitivity is explained by the fact that the alveolar epithelial type-II cells are rich with ACE-2. ACE-2 is a membrane-bound enzyme and a component of the renin-angiotensin system (RAS). It has a pivotal role in protecting the lungs against many of the acute respiratory injuries [11], by mediating the proliferation, fibrosis, and inflammation of the lung tissue [12].

The factors discussed above, i.e., the high affinity of SARS-CoV-2 to the ACE-2, as well as the abundance of these receptors in the lung epithelium and their protective role in these cells, all explain why the lungs are highly vulnerable to COVID-19 and are prone to a broad extent of pathological abnormalities [13]. Once the virus gains access to the lung tissue, it will initiate an inflammatory cascade as part of the innate immunity to combat the infection. However, this inflammatory activation also leads to severe pulmonary damage [14]. Among the many pro-inflammatory mediators that get stimulated with COVID-19, are different cytokines and chemokines of the innate immunity [15]. They get released at a fast rate recruiting large numbers of monocytes and dendritic cells to the lungs, exacerbating the inflammatory response and causing permanent fatal injury to the lungs. This phenomenon is otherwise known as a cytokine storm [16].

Moreover, the severity and pathogenicity of the infection could be correlated directly to the elevated levels of the released cytokines, which can also serve as biomarkers for infection [17]. This implies that the management of upregulated inflammation, which is a major cause of COVID-19 deaths, would significantly enhance the survival of the patients and avoid fatal complications. Hence, it is highly attractive to explore the interference with the cytokine storm as a therapeutic approach to tackle COVID-19. In this review, we provide a detailed insight into the cytokine storm phenomena as one of the key players to COVID-19 aggressiveness and progression. In addition, we discuss the potential therapeutic agents that could block or interfere with the cytokine storm, and provide a clinical update on their current status in COVID-19 treatment protocols. Moreover, we investigate the possible downfalls of such an approach and the optimum mean for its implication.

2. Interfering with the cytokine storm as an attractive therapeutic modality for COVID-19

After infection of the host with SARS-CoV-2, the body responds by initiating a rapid immune response involving the activation of different immune cells, such as T helper cells, Th1, Th2, Th17, macrophages, dendritic cells, and neutrophils [18]. Despite the fact that such immune activation is crucial as a first-line defense against the invading pathogen, nonetheless, the induced hyperactivation would result in abnormally high levels of pro-inflammatory chemokines and cytokines [19,20]. The accumulated cytokines constitute the storm phenomena that further empower the invasion of SARS-CoV-2 by sending signals which attract different immune cells. In turn, this results in a more sustained release of cytokines, initiating an aggressive inflammatory response and severe respiratory complications like ARDS [21–23]. Indeed, ARDS was documented to be caused and associated with elevated levels of cytokines, such as IL-6, IL-1β, IL-8. Therefore, the induced cytokine storm constitutes an inflammatory state that directly correlates with the leading cause of COVID-19 death [23]. Hence, targeting the elevated cytokines along with other pathways that aggravate the cytokines sustained release is an attractive approach to eliminate one of the hallmarks of COVID-19, and hopefully, reduce COVID-19 mortality rates (Fig.1). Under this aim, distinct cytokines stand out with specific functions related to COVID-19 pathogenesis. For instance, IL-1β was reported to be one of the cytokines of elevated levels and used as a biomarker for COVID-19 patients classification to mild, moderate, and severe cases [18]. Following the viral RNA recognition by the innate immune receptors, such as toll-like receptors (TLRs), they activate the nuclear factor of κB (NF-κB) to generate different cytokines, among which is tumor necrosis factor (TNF), and interleukins (IL): (IL-1β, IL-6, IL-18) [24]. IL-1β was reported in numerous studies to be one of the central mediators of lung damage and inflammation upon viral infection [25]. After SARS-CoV-2 recognition and induced secretion of IL-1β in its pro form, IL-1β will be activated by the action of caspase-1 to the mature IL-1β, afterwards, the mature form binds to its receptor IL-1R to activate subsequent signaling events that involve the activation of NF-κB transcription factor, c-Jun N-terminal kinase (JNK), and P38 mitogenic kinase [26] (Fig.1). These activated pathways will cooperate to induce IL-1 target gene expression, among which is another important cytokine, namely, IL-6 [27]. IL-6 is one of the major cytokines that promote acute inflammation [28]. This cytokine is prevalently expressed by nearly all stromal and immune cells. It is regulated by a variety of cytokines and pathways, among which are IL-1β and TNF-α [29]. Clinically, IL-6 was found to be significantly elevated in COVID-19 patients and correlating directly with the disease severity. Indeed, a study that investigated the levels of cytokines in 123 patients reported that serum IL-6 was significantly higher in patients suffering from a severe infection compared to patients with mild infection [30,31]. IL-6 plays a key role in the cytokine storm. It mediates its effects through two pathways, which are the cis (classical) and trans-signaling pathways. Once activated, both pathways initiate a cascade of events leading to the activation of the JAK-STAT and AKT/PI3K pathways [29,32]. IL-6 is also employed in an array of biological functions, including T cell clonal expansion, B cell differentiation, acute inflammatory response, and mitochondrial activity, etc. [29]. Another approach to attenuate the release of the cytokines is the inhibition of differentiation and activation of different T helper cells that promote the secretion of a wide stream of cytokines and chemokines. In fact, one of the major cellular pathways that govern T helpers' activation is the JAK-STAT pathway [33]. JAK-STAT can directly govern the differentiation of CD4 cells to the different T helpers, such as Th1, Th2, and Th17. Those cells play a pivotal role in the elimination of different viral and bacterial infections [34]. Therefore, using different Janus kinase (JAK) inhibitors will directly suppress the function of these T helper cells and the subsequent release of immune mediators. On the other hand, using JAK inhibitors is of advantage to counteract the signaling initiated from the elevated levels of Angiotensin-II in COVID-19 [35]. SARS-CoV-2 binding to ACE-2 results in the accumulation of Ang-II that can promote inflammation and vasoconstriction by the recruitment and activation of JAK on the angiotensin-1 receptor (AT1-R) [36]. Hence, Blocking JAK-STAT seems to play a dual role when it comes to COVID-19 pathogenesis, by counteracting elevated Ang-II and inhibiting different T helper cells.

One of the attractive targets that can utterly change the COVID-19 patients' prognosis is interfering with the activation of mast cells. Multiple studies reported documented evidence of crucial involvement of mast cells in the pathogenesis and progression of COVID-19 by further supplementing the infected tissue with a niche of pro-inflammatory cytokines [37]. Mast cells are hematopoietic cells that constitute a key part of the innate and adaptive immune system. They also possess specific pulmonary functions by releasing leukotrienes, histamines, and proteases. Thus, they contribute to allergic and pulmonary conditions [38]. Mast cells interact with the pathogen via a variety of innate surface pathogen recognition receptors (PRR) or cytosolic receptors that mediate mast cell activation, degranulation, and liberation of the different mediators [39]. Under constitutive activation, the released factors would damage the lung tissue, therefore targeting the mast cell mediators or using mast cell stabilizers to limit their degranulation might directly ameliorate the lung damage associated with SARS-CoV-2 (Fig.1).

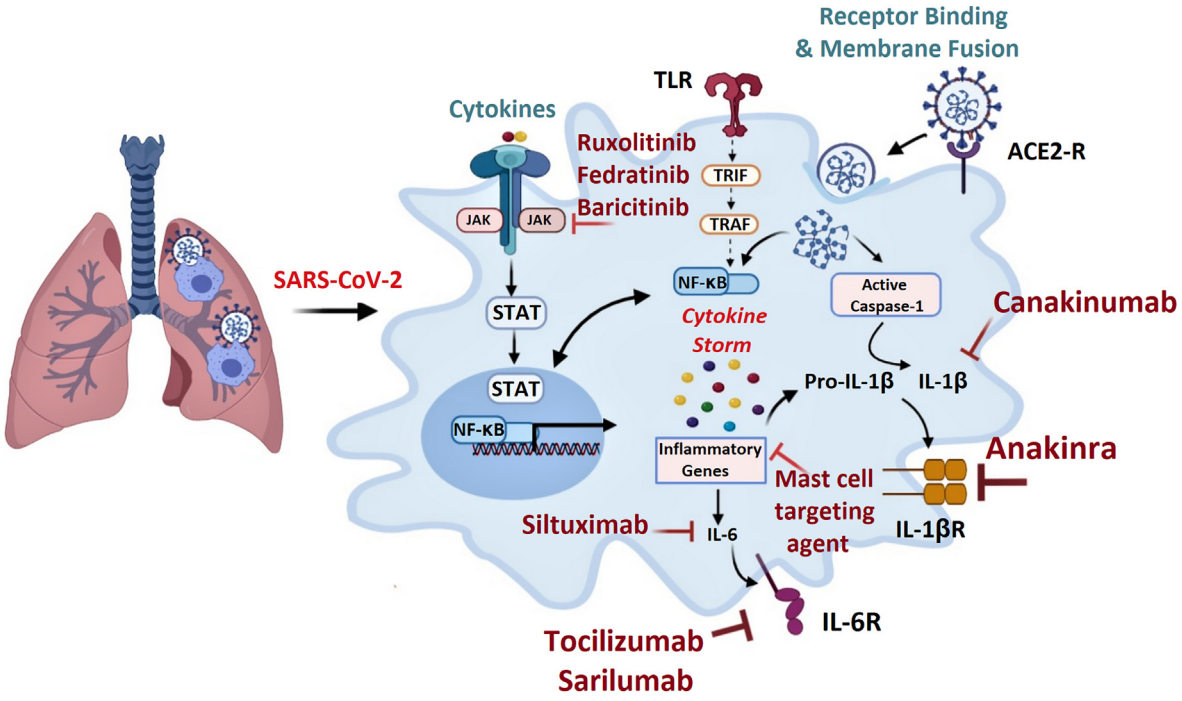

Fig. 1. Schematic diagram depicting the potential target pathways to counteract the cytokine storm. Once the SARS-CoV-2 invades the pulmonary epithelial cells, immune cells, such as mast cells recognize the viral RNA by their receptors, such as Toll-like receptors (TLR). This interaction activates transcription factors, such as NF-kB and STAT to ignite an inflammatory program harboring the cytokine storm. Among the different inflammatory products are the interleukins IL-1β, IL-6 that can promote further inflammation by interacting with corresponding receptors. Both the interleukins and their receptors can be targeted by the mentioned agents. JAK/STAT and mast cells can also be blocked to attenuate the constitutive inflammatory activation.

3. Therapeutic agents with the potential of interfering with COVID-19 associated cytokine storm

3.1. IL-6 inhibitors

IL-6 plays a pivotal role in activating several acute inflammatory responses, and thus their overexpression is a hallmark of cytokine storm [40]. Elevated levels of IL-6 were reported in COVID-19 patients in several studies [3,41–43]. Moreover, higher levels of IL-6 were found to be associated with more severe cases of COVID-19. In a retrospective study done on 452 COVID-19 patients at Tongji Hospital in Wuhan, IL-6 levels were significantly higher in COVID-19 patients in critical conditions [41]. Similar results were reported in two other hospitals where they found higher levels of IL-6 in non-survivors compared to survivors of COVID-19 [41]. Consequently, a very promising approach that is currently undergoing trials is targeting the cytokine storm in COVID-19 patients via IL-6 inhibitors like tocilizumab (Table 1), sarilumab, and siltuximab (Table 2).

3.1.1. Tocilizumab

Tocilizumab is a humanized anti–IL-6 receptor monoclonal antibody. It is a competitive inhibitor of both the membrane-bound and soluble IL-6 receptor, thus inhibiting both the cis and trans transduction pathways of IL-6 [44]. It was first approved as a therapeutic agent for rheumatoid arthritis [45], and in 2017 it was also approved to treat cytokine release syndrome in patients undergoing chimeric antigen receptor (CAR) T cell therapy [46].

Several cohort studies demonstrated the efficacy of tocilizumab in treating severe cases of COVID-19 and normalizing fever, C-reactive protein (CRP) levels, and lymphocyte counts in most patients. As abnormal CRP levels, lymphocyte counts, ferritin levels, and D-dimer levels are hallmarks of cytokine storm; tocilizumab seems promising as a treatment for COVID-19 associated cytokine storm [47–49].

A study was done in 2 hospitals in Anhui province, China, on 21 patients recruited with either severe or critical cases of COVID-19. Patients were treated with either a single dose or two doses 12 h apart of tocilizumab along with standard therapy. Following the administration of tocilizumab, fever was resolved in all patients on the first day. Within five days of treatment, 84.2% of patients experienced a remarkable reduction of CRP levels back to normal, and 75% of patients showed an improvement in oxygen saturation and required less oxygen support. All patients were eventually discharged with no serious adverse effects due to tocilizumab [47]. Another retrospective study was done in Tongji hospital on 15 patients with their cases varying from moderately to critically ill. Patients received one or more doses of tocilizumab. A significant reduction in CRP levels was reported for all patients except one. However, three critically ill patients who received only a single dose of tocilizumab still died within a week. In these patients, a high level of IL-6 was observed that was not ameliorated like in the other patients with better outcomes. In the study, elevated CRP levels and IL-6 levels were linked to disease aggravation. Ten patients out of the 15 were able to reach clinical stabilization. The researchers concluded that in critically ill patients, a single tocilizumab dose was not enough to achieve clinical stabilization [49]. In Qatar, another retrospective study was conducted on twenty-five COVID-19 patients admitted to the intensive care unit (ICU) who have been given at least one dose of tocilizumab. Patients in this study also experienced a remarkable decrease in fever and CRP levels. There was a marked decrease in the number of patients needing invasive oxygen therapy after 14 days of tocilizumab's administration. Three out of twenty-five patients in the study died, which was reported to be a lower mortality rate compared to other cohort studies done on critically ill COVID-19 patients. This, however, could be partly attributed to the relatively low median age (58 years) and the low number of comorbidities in patients of this study. Notably, in this study, a third of the patients had candida species in their respiratory cultures, and one patient had a case of herpes simplex virus reactivation [48]. Though it was not confirmed that these infections were related to tocilizumab administration, this

Table 1
Summary of selected clinical trials investigating tocilizumab in COVID-19.

Recruiting status	Number of centers, study design	Country	Population (*n* of COVID-19 positive patients)	Intervention group(s)	Comparison group(s)	Primary outcome(s)	NCT number
Recruiting (phase 2)	Multicentered, open-labeled	Spain	$n = 500$	IV tocilizumab	–	Time of intubation, time with oxygen therapy and non-invasive mechanical ventilation Mortality rate [time frame: average of 1 month]	NCT04445272
Recruiting (phase 2)	Multicentered, open-labeled, randomized	Spain	$n = 276$	Tocilizumab + hydroxychloroquine +azithromycin	Hydroxychloroquine +azithromycin	In-hospital mortality Need for mechanical ventilation [time frame: average of 2 weeks]	NCT04332094
Recruiting (phase 2)	Single center, open-labeled, randomized	Spain	$n = 78$	IV tocilizumab 8 mg/kg one dose Or IV tocilizumab 8 mg/kg two doses	Standard of care	Average increase in IL-12 values [time frame: day 1 and day 3]	NCT04435717
Recruiting (phase 3)	Open-labeled, RCT	Brazil	$n = 150$	Single-dose IV tocilizumab 8 mg/kg	Best supportive care	Clinical status of the patients [time frame:15 days]	NCT04403685
Not yet recruiting (phase 3)	Multicentered, open-labeled, randomized	Tunisia	$n = 260$	IV tocilizumab 8 mg/kg + enoxaparin 4000 IU	Deferoxamine + enoxaparin 4000 IU	Mortality rate [time frame: 90 days]	NCT04361032
Recruiting (phase 3)	Double blinded, RCT	US	$n = 300$	IV tocilizumab 8 mg/kg	IV placebo	Clinical status assessed using a 7-point ordinal scale [time frame: 28 days]	NCT04412772
Not yet recruiting (phase 2)	Single center, open-labeled, RCT	Sweden	$n = 120$	4 doses of 100 mg IV anakinra per day for 7 days + standard of care Or 8 mg/kg single IV infusion of tocilizumab+ Standard of care	Standard of care	Time to recovery [time frame: 29 days]	NCT04412291
Not yet recruiting (phase 3)	Open-labeled, randomized	France	$n = 216$	Anakinra + tocilizumab Or anakinra + tocilizumab + ruxolitinib	Standard of care	Ventilation free days [time frame: 28 days]	NCT04424056
Recruiting (phase 3)	Multicentered, double blinded, randomized	US	$n = 450$	IV remdesivir + IV tocilizumab	IV remdesivir + IV placebo	Clinical status assessed using a 7-category ordinal scale [time frame: 28 days]	NCT04409262
Recruiting (phase 2)	Open-labeled	US	$n = 217$	IV tocilizumab	–	Clinical outcome evaluated by a 7-category clinical status ordinal scale [time frame: at least 60 days, up to 1 year]	NCT04370834
Recruiting (phase 2)	Open-labeled, RCT	Spain	$n = 24$	8 mg/kg IV tocilizumab +200 mg IV pembrolizumab	Standard of care	Percentage of patients with normalization of $SpO_2 \geq 96\%$ on room air [time frame: 14 days]	NCT04335305
Recruiting (phase 3)	Open-labeled, randomized	Belgium	$n = 342$	Tocilizumab or tocilizumab + anakinra or siltuximab or siltuximab + anakinra	Standard of care	Time to clinical improvement [time frame: 15 days]	NCT04330638
Recruiting	Multicentered, open-labeled, RCT	China	$n = 150$	Favipiravir + tocilizumab	Favipiravir alone or tocilizumab alone	Clinical cure rate [time frame: 3 months]	NCT04310228

Abbreviations: **RCT**, randomized controlled trial; **US**, United States; **IV**, intravenous; **IU**, international units; **IL-12**, interleukin 12.

Table 2
Summary of clinical studies investigating the implications of the mentioned agents in COVID-19 patients.

Drug	Recruiting status	Number of centers, study design	Country	Population (number of COVID-19 positive patients)	Intervention group(s)	Comparison group(s)	Primary outcome(s)	NCT number
Anakinra	Recruiting (phase 3)	Multicentered, open-labeled, randomized	France	n = 240	IV Anakinra for 7 days + standard therapy	Standard treatment	Treatment success at day 14	NCT04364009
Tocilizumab	Recruiting (phase 3)	Multicentered, RCT	USA, Canada, others	n = 330	1 dose of IV of Tocilizumab	1 dose of IV placebo	Clinical Status Assessed Using a 7-Category Ordinal Scale	NCT04320615
Sarilumab	Recruiting (phase 2/3)	Multicentered, RCT	USA	n = 400	1 dose of IV sarilumab (high dose) or 1 dose of IV sarilumab (low dose)	1 dose of IV placebo	Percent change in CRP levels Improvement in clinical status in patients with high serum IL-6 levels	NCT04315298
Siltuximab	Recruiting (phase 2)	Multicentered, open-label, randomized	Spain	n = 200	A single dose of IV siltuximab	IV infusion of methylprednisolone for 6 days	The proportion of patients requiring ICU admission	NCT04329650
Baricitinib	Recruiting (phase 4)	Randomized, parallel-arm, open-label platform trial.	UK	n = 1167	Baricitinib + standard of care or ravulizumab + standard of care	Standard of care	Time to the incidence of the composite endpoint of: Death, mechanical ventilation, cardiovascular organ support, or renal failure	NCT04390464
Ruxolitinib	Recruiting (phase 3)	Multicentered, RCT	USA	n = 500	Ruxolitinib 5 mg BID Or Ruxolitinib 15 mg BID	Placebo BID	The proportion of participants who have died due to any cause	NCT04377620
Hydroxychloroquine	Active, not recruiting (phase 2/3)	Multicentered, RCT	USA	n = 58	HCQ orally for 4 days.	Placebo for 4 days.	% of negative PCR swabs after 7 days	NCT04353271
Hydroxychloroquine	Active, not recruiting (phase 2)	Non-randomized	USA	n = 228	HCQ orally 400 mg BID on day 1, followed by 400 mg once a week for a total of 7 weeks.	No intervention	Rate of COVID-19 positive conversion [time frame: 7 weeks]	NCT04333225
Hydroxychloroquine	Not yet recruiting (phase 4)	Single center, RCT	USA	n = 120	HCQ orally	Standard treatment	Clinical recovery time	NCT04382625
Quercetin	Recruiting	Multicentered, non-randomized	Turkey	COVID-19 negative with no history and COVID-19 positive n = 50	Quercetin prophylaxis orally 500 mg. (COVID-19 negative) Quercetin orally 1000 mg (COVID-19 positive)	No intervention	Prevalence of COVID-19 calculated using a questionnaire. Standardized mortality rate.	NCT04377789
Montelukast	Not yet recruiting (phase 3)	Multicentered, RCT	Canada	n = 600	10 mg oral montelukast once daily for 60 day	Placebo	Emergency room visits and hospitalizations [time frame: 12 weeks]	NCT04389411
Infliximab	Recruiting	Multicentered, prospective cohort	France	n = 850	IV infusion of infliximab or vedolizumab	–	Impact of IgG and IgM on the risk of viral infection [time frame: 2 years]	NCT04344249
Camostat Mesylate	Not yet recruiting (phase 2)	RCT	USA	n = 144	Camostat mesylate 200 mg for 7 days.	Placebo for 7 days	Clinical recovery time	NCT04353284
Hydroxychloroquine Azithromycin Ivermectin Camostat mesilate	Recruiting (phase 2)	RCT	USA	n = 240	Group 1: HCQ Group 2: HCQ and azithromycin Group 3: HCQ and ivermectin - Group 4: Camostat mesilate	–	Clinical deterioration [time frame: 14 days]	NCT04374019
Dexamethasone	Recruiting (phase 2/3)	Multicentered, open-label, randomized	UK	n = 12,000	Low dose of dexamethasone or prednisolone	Standard treatment	All-cause mortality rate within 28 days	NCT04381936
Dexamethasone	Recruiting (phase 4)	Multicentered, open label, randomized	Spain	n = 200	Standard intensive care + dexamethasone	Standard intensive care	All-cause mortality at 60 days after enrollment	NCT04325061
IVIG	Recruiting (phase 3)	Multicentered, RCT	France	n = 138	IVIG infusion over 4 days	Placebo (0.9% NaCl) infusion over 4 days	Ventilator-free days	NCT04350580
Prazosin	Recruiting (phase 2)	Open-labeled, randomized	USA	n = 220	Prazosin	Standard treatment	-Number of deaths - Number of participants requiring mechanical ventilation or ICU admission	NCT04365257

(*continued on next page*)

Table 2 (*continued*)

Drug	Recruiting status	Number of centers, study design	Country	Population (number of COVID-19 positive patients)	Intervention group(s)	Comparison group(s)	Primary outcome(s)	NCT number
Telmisartan	Not yet recruiting (phase 2)	Open-labeled, randomized	Argentina	n = 400	80 mg telmisartan BID + standard treatment	Standard treatment	CRP levels	NCT04355936

RCT, randomized controlled trial; **CRP**, C-reactive protein; **IL-6**, interleukin 6; **ARDS**, acute respiratory distress syndrome; BID, twice daily; **HCQ**, hydroxychloroquine; **IgG**, immunoglobulin G; **IVIG**, intravenous immunoglobulins.

still raises the concern of whether short-term use of tocilizumab could also be associated with opportunistic infections. Similar observations were reported in Italy, where 3 out of 43 patients with severe COVID-19 pneumonia treated with tocilizumab developed candidemia [50]. In a prospective open, single-arm study done in Italy, 63 patients with severe cases of COVID-19 were administered tocilizumab either once or twice with doses taken 24 h apart. Within a day, a marked reduction in fever was observed in all patients except one and levels of CRP, ferritin, lymphocyte count and D-dimer were improved in most patients. There was also a significant improvement in the respiratory function of patients within two weeks, with no reported serious adverse effects due to tocilizumab [51]. Another prospective study was done on 100 COVID-19 patients with acute respiratory failure in Italy. They were given two doses of tocilizumab 12 h apart. Within ten days, the respiratory conditions of 77 patients were significantly improved, and a notable enhancement in CRP, lymphocyte count, and ferritin levels were observed in most patients, especially those with improved outcome. However, 23 patients suffered worsening of their respiratory functions, and 20 of them died. Serious adverse events were reported in three patients. Among them, two patients experienced septic shock, and one patient had gastrointestinal perforation [52].

Several single-case studies have also reported the success of tocilizumab in treating patients with severe COVID-19 suffering from varying comorbidities, such as metastatic renal cell carcinoma [53], sickle cell disease [54,55], multiple myeloma [56], and end-stage renal disease [57]. Nevertheless, one case report described two COVID-19 patient cases who, despite their treatment with tocilizumab, developed secondary hemophagocytic lymphohistiocytosis (sHLH), which is a severe form of cytokine release syndrome. One of these patients also developed viral myocarditis after tocilizumab administration [58]. In another case study, hypertriglyceridemia was observed in two patients treated with tocilizumab [59]. These emerging findings suggest that tocilizumab could be a promising agent in treating cytokine storm in patients with severe cases of COVID-19. This encouraged China and Italy to include tocilizumab in their national guidelines for treating severe COVID-19 cases [60,61]. We should not disregard, however, that all results came from uncontrolled studies with small sample size. Also, some serious adverse effects were observed in a small subset of treated patients. Hence it is still too soon to make conclusions about tocilizumab and its efficacy or the frequency of adverse events associated with its use.

For this reason, several clinical trials have been announced worldwide to assess the effectiveness of tocilizumab in COVID-19. In China, a phase 4 multi-centered, randomized controlled trial for the efficacy and safety of tocilizumab in COVID-19 pneumonia is currently ongoing (ChiCTR2000029765). Genetech, Inc. launched a phase 3 randomized, double-blinded, placebo-controlled, clinical trial to evaluate the efficacy and safety of tocilizumab in COVID-19 patients with pneumonia and is expected to enroll 379 patients in this study (NCT04372186). Another phase 3 randomized, double-blinded clinical trial for the same purpose will also take place in several centers in the United States, Canada, United Kingdom, Italy, Spain, France, Germany, Netherlands, and Denmark (NCT04320615). Additionally, there are currently many clinical trials involving tocilizumab either alone or in combination with other drugs for the treatment of COVID-19 that are registered in clinicaltrials.gov database (Table 1).

3.1.2. Sarilumab

Sarilumab is another anti–IL-6 receptor monoclonal antibody with a higher affinity than tocilizumab; it is approved for the treatment of rheumatoid arthritis both subcutaneously and intravenously. It also inhibits both the cis and trans transduction pathways of IL-6 signaling through competitive inhibition of both the membrane-bound and soluble IL-6 receptors [62]. Sarilumab demonstrated promising potential in improving COVID-19 patients' symptoms, as indicated by the clinical findings reported by Benucci et al. [63]. The addition of sarilumab to

the therapy regimen of eight hospitalized COVID-19 positive patients showed significant improvement in the respiratory functions by reducing oxygen demand by 30%. Moreover, early and aggressive intervention in these patients with IL-6 blockers resulted in their discharge after 14 days of hospitalization, and seven out of them tested back negative for COVID-19 [63]. Further elucidation on sarilumab efficacy in COVID-19 therapy is expected to be revealed with different clinical trials, such as a phase 2/3, randomized, double-blind, placebo-controlled clinical trial that was launched to assess the efficacy and safety of sarilumab in hospitalized COVID-19 patients (NCT04315298) (Table 2). Around 400 patients are expected to be recruited in this study. Seven other clinical trials are registered on the clinicaltrials.gov database to study the efficacy and safety of sarilumab in COVID-19 patients (NCT04386239, NCT04357860, NCT04357808, NCT04345289, NCT04327388, NCT04324073, NCT04322773).

3.1.3. Siltuximab

Siltuximab is a chimeric human-mouse anti-IL-6 monoclonal antibody. It binds directly to soluble IL-6 and prevents it from acting on IL-6 receptor to activate the IL-6 signaling pathways. It is currently approved by the Food and Drug Administration (FDA) for the treatment of multicentric Castleman disease [64]. Some centers are presently also studying the effects of siltuximab in COVID-19 patients. Positive preliminary data have been reported by one center in Italy, conducting an observational case-control study on the use of siltuximab in patients diagnosed with COVID-19 pneumonia (NCT04322188). Results from 21 COVID-19 patients admitted in this study with respiratory complications showed that after siltuximab administration, CRP levels were reduced remarkably in most patients. 33% of patients showed an improvement in their condition and no longer required ventilatory assistance, 44% were in a stable condition, and 24% experienced worsening in their condition [65]. Along with this study, a phase 2 and a phase 3 trial involving siltuximab have been registered in clinicaltrials.gov database (NCT04329650, NCT04330638) (Table 2).

3.2. IL-1 inhibitors

The pro-inflammatory cytokines in the IL-1 family are one of the regulators of IL-6 production, and hence elevated levels of IL-1 cytokines are another hallmark of the cytokine storm [66]. High levels of IL-1β and its endogenous antagonist, IL-1 receptor antagonist (IL-1 Ra) have been associated with cytokine storm and hemophagocytic lymphohistiocytosis (HLH) [67]. Elevated levels of these cytokines were also reported in COVID-19 patients [18]. Hence, IL-1 inhibition is another attractive method being tested for attenuating cytokine storm in COVID-19 patients. The primary drug currently being studied for this purpose is anakinra.

3.2.1. Anakinra

Anakinra is the recombinant form of the endogenous IL-1Ra. It blocks the binding of IL-1β and IL-1α to their receptor IL-1R and hence blocks IL-1 activity [68]. It is FDA approved for treating rheumatoid arthritis, and its benefits have also been explored in the management of hemophagocytic lymphohistiocytosis, macrophage activation syndrome (MAS), and sepsis [69]. Recently, a case report outlined the success of using anakinra to reverse the cytokine storm due to MAS when previously tried immunomodulators like methylprednisolone and cyclosporine have failed [70]. This could hint to the benefits that IL-1 blockers could bring to the management of cytokine storm in COVID-19 patients.

In fact, several studies have reported the potential benefit of anakinra for COVID-19 patients. In a small open-label study done in France, anakinra was administered subcutaneously to nine patients with COVID-19 pneumonia for ten days. Within eleven days, CRP levels were normalized in five patients, and CT scans in all patients showed no extension of the pulmonary lesions. It should still be noted that following anakinra's administration, a mild elevation in transaminase and triglyceride levels was observed in some patients; however, this could possibly be attributed to sHLH manifestations in these patients [71]. Another pilot study done on five patients who were administered anakinra in Italy demonstrated favorable results, as all patients experienced an improvement in their respiratory functions and a quick resolution of their systemic inflammation without any observed serious adverse effects [72]. To further confirm these results, an open-label trial in Italy has been launched (NCT04324021). Another study was conducted to assess the outcomes of seven ICU and one non-ICU COVID-19 patients with acute respiratory failure and sHLH. Following their treatment with intravenous doses of anakinra for seven days, all seven ICU patients showed an improvement in their respiratory functions and reduction in sHLH symptoms. Three patients, however, died due to refractory shock. Though this death rate might appear high, the study reported that death rates with sHLH could reach up to 67%. The non-ICU patient in this study was a 71 years old female presenting with comorbidities, such as cancer and hypertension. Upon deterioration in her clinical condition and exhibiting respiratory difficulties, the patient was given anakinra for four days. A day after the first anakinra administration, the patient showed immediate improvement in respiratory function and recovery from sHLH manifestations. As a result, she was discharged nine days after anakinra administration [73].

The study with the largest sample size to this date that was published is a retrospective cohort study that took place in Milan on 29 COVID-19 patients with ARDS and hyperinflammation. The group treated with anakinra experienced a significant reduction in CRP levels, a better improvement in respiratory functions, and a higher cumulative survival rate (90%) compared to the standard treatment group (56%). Anakinra was discontinued in seven patients due to the appearance of adverse effects in these patients (bacteremia and elevations in liver aminotransferase levels). These adverse effects were also observed in the standard treatment group [74].

All these studies support the potential use of anakinra in the subset of COVID-19 patients presenting with cytokine storm manifestations. However, there are still some questions that need to be answered, such as at what stage of the disease would be the most suitable for giving anakinra?, what dosage and route of administration would give the most benefit?, whether anakinra could be used as a replacement for tocilizumab or in combination, and whether there are any unreported adverse effects. For these reasons, controlled clinical trials with sufficient sample size are a must to determine the actual value of IL-1 inhibition. Up to date, there are eight clinical trials related to anakinra registered in clinicaltrials.gov database taking place worldwide (NCT04366232, NCT04341584, NCT04362943, NCT04362111, NCT04357366, NCT04339712. NCT04330638, NCT04324021).

3.2.2. Canakinumab

Along with anakinra, canakinumab is another IL-1 inhibitor. It is an anti- IL-1β monoclonal antibody. A few published studies show the potential benefit that canakinumab could bring to clinics. The first one is a case study of a 70-year-old woman who was diagnosed with cryopyrin-associated periodic syndrome and received canakinumab as a treatment for her case. Ten days after receiving her periodic dose, she developed COVID-19 symptoms and tested positive. Even though she would have been classified as a high-risk patient for developing serious complications due to her age and being on immunosuppressive medications, her symptoms appeared to be mild, and in a couple of days, they resolved [75]. This suggests that interleukin blockade by canakinumab could have possibly prevented the progression of COVID-19. Another study that demonstrated the positive effects of canakinumab was conducted on ten COVID-19 patients presenting with signs of hyper-inflammation and respiratory failure. They were administered a single subcutaneous dose of canakinumab along with standard therapy, and their clinical outcomes were retrospectively compared with ten other patients treated previously with the same standard therapy

without canakinumab. The canakinumab group showed a remarkable decrease in CRP levels and rapid improvement in oxygenation compared to the standard treatment group. Moreover, patients treated with canakinumab did not display any serious systemic adverse events or signs of severe immunosuppression [76]. Even though the data is limited, they collectively point to the potential of canakinumab as a safe and effective treatment for attenuating cytokine storm symptoms of COVID-19 patients. It would still be important to evaluate its true efficacy further and compare it to other IL-1 blockers like anakinra. Canakinumab is currently being tested in phase 2 and a phase 3 clinical trial in COVID-19 patients (NCT04365153, NCT04362813). It is also being tested in an observational cohort study in Italy (NCT04348448).

3.3. JAK inhibitors

Another attractive approach to target the cytokine storm is through JAK-STAT pathway inhibition, which interferes with the signaling of several cytokines at once. This approach could offer an advantage over IL-6 and IL-1 inhibitors, as many cytokines are involved in the pathogenesis of COVID-19 associated cytokine storm. Researchers have especially shown keen interest in JAK2 inhibitors for the involvement of JAK2 signaling in the activation of IL-6 and Th17 associated cytokines, which play a significant role in COVID-19 associated cytokine storm [77]. Some of the JAK inhibitors being discussed for the treatment of COVID-19 are baricitinib, ruxolitinib, and fedratinib.

3.3.1. Baricitinib

Baricitinib is an orally administrated selective JAK1/JAK2 inhibitor that is FDA-approved for the treatment of patients with moderate to severe rheumatoid arthritis [78]. Through its mechanism, it can interfere with the signaling of several cytokines that are overexpressed in COVID-19 patients like IL-2, IL-6, IL-7, and granulocyte-macrophage colony-stimulating factors (GM-CSF) [41]. Richardson et al. also suggested another mechanism through which baricitinib could be beneficial in the treatment of COVID-19. By using artificial intelligence and algorithms to identify potential candidate treatments for COVID-19, they identified baricitinib as an AP2-associated protein kinase 1 (AAK1) inhibitor, thus hinting at its potential to inhibit viral entry and assembly inside cells [79]. Both its potential antiviral and anti-inflammatory properties make baricitinib an interesting therapeutic option for COVID-19 patients. However, there were several concerns raised about its use. One concern is that JAK-STAT signaling pathway is necessary for an interferon-mediated antiviral response. Hence, its inhibition poses the risk of increasing the viral load in infected patients [80]. Another concern is the safety profile of baricitinib and other JAK inhibitors, as there is a risk of thromboembolism with their use. COVID-19 patients, specifically those with hyper inflammation and cytokine storm symptoms, develop coagulation abnormalities, thus administering these medications might aggravate this issue [81].

Clinical trials are already being conducted to study the safety and efficacy of baricitinib in COVID-19 treatment. Preliminary results were published from one open-label study done in Italy to assess the outcomes of patients with moderate cases of COVID-19 pneumonia administered baricitinib (NCT04358614). In this study, the outcomes of twelve patients who received baricitinib along with standard therapy were compared to the outcomes of twelve other patients who previously received standard therapy alone. The results showed a significant improvement in the CRP levels, oxygen saturation levels, and fever in the baricitinib treated group compared to the standard group. None of the patients on baricitinib were admitted to the ICU during the study, whereas four patients from the standard group required transferring to the ICU. Within two weeks, 58% of the baricitinib treated group was discharged compared to 8% of the standard therapy group. In this study, baricitinib was well tolerated by the patients and did not cause serious adverse effects [82]. Though the results are promising, they are not enough to confirm the safety and efficacy of baricitinib due to the open-label design of the study and the insufficient sample size. Hence, more trials are warranted to be able to make better conclusions about baricitinib. Along with this study, there are currently nine clinical trials registered in the clinicaltrials.gov database to assess the benefits of baricitinib (NCT0439305, NCT04390464, NCT04373044, NCT04362943, NCT04346147, NCT04345289, NCT04340232, NCT04321993, NCT04320277).

3.3.2. Ruxolitinib and fedratinib

Similar to baricitinib, ruxolitinib is a selective JAK1 and JAK2 inhibitor. It is indicated for the treatment of patients with myelofibrosis [83]. Ruxolitinib demonstrated promising results as a treatment option for patients with sHLH in an open-label pilot study, which could indicate its potential in treating COVID-19 patients as well with hyper-inflammatory complications [84]. Fedratinib is a highly selective inhibitor of JAK2 and also a modest inhibitor of JAK1 and JAK3, which received its first FDA approval in 2019 for the treatment of patients with myelofibrosis [85]. When tested on murine Th17 cells, fedratinib caused suppression in the expression of Th17 associated cytokines, and therefore could potentially aid in managing COVID-19 associated cytokine storm [77]. Unlike baricitinib, both fedratinib and ruxolitinib do not seem to exhibit antiviral properties as they did not show a high affinity to AAK1 [79]. Regardless, clinical trials have been launched for ruxolitinib to evaluate its value as a COVID-19 treatment. There are currently 14 clinical trials registered on clinicaltrials.gov related to ruxolitinib (NCT04348695, NCT04361903, NCT04331665, NCT04338958, NCT04348071, NCT04359290, NCT04355793, NCT04366232, NCT04354714, NCT04362137, NCT04377620, NCT04334044, NCT04374149, NCT04337359).

3.4. Chloroquine/hydroxychloroquine

Chloroquine (CQ) has long been used for prophylaxis and treatment of malaria [86]. Hydroxychloroquine (HCQ) sulfate salt is more soluble and much less toxic metabolite of CQ. It is used as an antimalarial agent, and it has wide applications in autoimmune diseases, such as rheumatoid arthritis, juvenile idiopathic arthritis and systemic lupus erythematosus [87]. The use of CQ and HCQ in the treatment of SARS-CoV-2 infection was implemented early in the outbreak in China. CQ and HCQ were shown as potentially effective treatments for COVID-19 and were effective in lowering the disease mortality rates [31,88]. In addition to their antimalarial activity, they possess a potent anti-inflammatory activity that may suppress the cytokine storm in SARS-CoV-2 infected patients. CQ and HCQ interfere with lysosomal activity and inhibit their function, resulting in reduced expression of the major histocompatibility complex class II (MHC II), and impaired antigen presentation [89], thus decreasing T cell activation and expression of co-stimulatory proteins [90]. This will decrease the production and release of various pro-inflammatory cytokines, including TNF, IL-1, IL-6, and interferon-α (IFN- α) [91], the major mediators of the cytokine storm syndrome.

In the current outbreak, the use of CQ and HCQ received colossal attention. On March 28, 2020, the US-FDA granted Emergency Use Authorization (EUA) to be included in the treatment protocol for COVID-19, despite that there were no strong and enough randomized controlled trials to support their use in regards to their safety and efficacy profiles [92]. The antiviral activity of CQ and HCQ has been reported in several previous studies targeting a wide range of viruses, including human immunodeficiency virus (HIV), Ebola virus, and SARS-CoV [93–95]. Besides their anti-inflammatory and immunomodulatory effects, the main benefit of using CQ and HCQ in SARS-CoV-2 infection is attributed to their antiviral activity. Although both CQ and HCQ showed promising *in vitro* results in controlling SARS-CoV-2 infection, HCQ was more potent with half-maximal effective concentration (EC_{50}) of 0.72 μM, which was more than CQ with EC_{50} of 5.47 μM *in vitro* [56,96].

Several studies revealed possible mechanisms by which CQ and HCQ act as antiviral agents against SARS-CoV-2. CQ inhibits the binding of SARS-CoV to ACE-2 by interfering with the glycosylation process. As a result, the cellular entry and infection with the virus are inhibited [95]. Due to the similarity in structures between SARS-CoV and SARS-CoV-2, as the latter also use ACE-2 for its entry, a similar effect of CQ on SARS-CoV-2 is anticipated [97]. Furthermore, CQ increases lysosomal and endosomal pH [89,95], thus disrupting the cleavage of SARS-CoV surface spike proteins and fusion steps, which are necessary for viral replication and infection [98,99]. In addition, CQ significantly decreased human coronavirus 229E (HCoV-229E) replication through inhibiting the activation of p38 mitogen-activated protein kinases (MAPK) and extracellular-signal-regulated kinase (ERK) pathways [100]. Given that HCQ and CQ have a similar chemical structure, it is highly possible that HCQ will perform the same mechanisms of CQ in terms of activity and disease progression.

It is worth mentioning that both CQ and HCQ can display an extended spectrum of activity against COVID-19 by having direct interference with cytokine storm, which can synergize with their antiviral activity and empower their implementation in early and late-stage SARS-CoV-2 infection. They showed promising results in ameliorating SARS-CoV-2 induced pneumonia with improvement in lung imaging findings and a shorter disease course, thus reducing the length of hospital stay [31,101]. However, there is a dilemma concerning their use and safety. CQ and HCQ, in general, are associated with several side effects, such as gastrointestinal and hepatic complications [102,103], and the most concerning one; is the possibility of QT prolongation, which at some point could be exaggerated and lead to life-threatening arrhythmia [104,105]. A recent retrospective cohort study in the Netherlands was conducted to assess the degree of CQ-induced QTc prolongation in SARS-CoV-2 patients. In a total of 95 patients, CQ significantly prolonged the QTc interval; this highlights the need for careful monitoring and recording of ECG during CQ therapy [106]. This becomes more crucial when CQ is administered in combination with another medication that is known to induce QT prolongation and increase the risk of torsades de pointes, like azithromycin [107,108]. For this reason, on April 30, 2020, the FDA warned against the use of CQ or HCQ for COVID-19 outside of a hospital or a clinical trial setting [109]. Besides, a case series described three cases of critically ill SARS-CoV-2 patients who developed methemoglobinemia while receiving HCQ [110]. It was not clear if this serious side effect was strictly related to HCQ intake or due to SARS-CoV-2 complications [110]. However, considering that the oxidizing properties of HCQ and methemoglobinemia have not been described as a complication of SARS-CoV-2, HCQ would be the most probable cause.

At this moment, dozens of clinical trials are ongoing worldwide to evaluate the safety and efficacy of CQ and HCQ in SARS-CoV-2 infection [111]. In addition, many trials are evaluating their use as potential prophylactic therapy [112]. Some of those recent clinical trials are listed in Table 2. Several trials have already reported important results concerning the effectiveness and safety of CQ and HCQ in treating SARS-CoV-2. In China, a randomized open-label trial assessed the efficacy and safety of HCQ in comparison with standard treatment in 150 hospitalized SARS-CoV-2 patients [113]. The results revealed that after 28 days, there was no significant difference in the probability of virus elimination between HCQ and standard care. In regard to safety, adverse events were higher in the HCQ group. The most common adverse event in both groups was diarrhea in 21 (30%) patients of HCQ group, compared with 7 (9%) patients in the standard of care group. Two patients developed serious adverse events in HCQ group due to disease progression and upper respiratory tract infection [113]. Overall, the results of this study did not support the use of HCQ in patients with SARS-CoV-2. Another randomized trial was conducted in Brazil to evaluate the safety and efficacy of high- and low-dosage CQ in 440 patients with severe SARS-CoV-2 infection [114]. Mortality by 13 days was 39% and 15% in the high- and low-dosage groups, respectively. Furthermore, ~19% of the patients in the high-dosage group presented QTc interval > 500 ms in comparison with 11% in the low-dosage group. These findings suggest that a higher dosage of CQ in critically ill patients is not highly recommended due to the potential risk and could be fatal at some point [114]. Based on the preliminary results, it is difficult to make a clear decision regarding the use of CQ and HCQ in the treatment of SARS-CoV-2. As there was no strong evidence to believe that CQ and HCQ may be effective and, at the same time, safe in treating COVID-19 patients, consequently, on June 15, 2020, the FDA revoked the Emergency Use Authorization for CQ and HCQ [115].

3.5. Targeting mast cells

Mast cells (MCs) and their products are well known for their dominant role in inflammatory and allergic reactions when activated by pathogens, including viruses [116], as well as their involvement in innate and acquired immunity [117]. Emerging coronaviruses are known to cause ARDS or vascular leakage through excessive MC activation [118]. MCs may get activated by SARS-CoV-2 through TLRs or by the induction of IgE-FcεRI crosslinking [119]. Subsequently, activated MCs secrete pro-inflammatory cytokines and bronchoconstrictor mediators, leading to a fatal inflammatory response and pulmonary complications that contribute to SARS-CoV-2 disease severity [18]. Hence, there is an intense need to prevent and control mast cell mediators release or to inhibit the actions of those mediators once released into the environment.

3.5.1. Mast cell stabilizers

The suppression of MC activity by MC stabilizers may alleviate all the complications accompanied by a cytokine storm in SARS-CoV-2 infection. MC stabilizers exert their effect by blocking mast cell degranulation and preventing the release of histamine and related mediators. MC stabilizers showed their potential in increasing survival and improving disease outcomes in wild type mice infected by Dengue virus (DENV) and influenza A virus models [120,121]. They have a broad effect of reducing inflammatory cytokines release in multiple cell types, which suggests their potential benefit in downregulating the status of hypercytokinemia in SARS-CoV-2 infection. Many drugs belong to this class, including cromolyn, ketotifen, quercetin, and luteolin.

Cromolyn sodium is an anti-inflammatory agent used in the treatment of MC-related disorders. It is commonly used for prophylactic treatment of asthma, mastocytosis, allergic rhinitis, and conjunctivitis [122]. It prevents mast cell activation and degranulation and therefore inhibits the release of inflammatory mediators, exerting its action by inhibiting protein kinase C activity and chloride transport into the mast cells [123]. It also blocks macrophage activation, the release of eicosanoids and cytokines, as well as adhesion molecule expression [124]. In H5N1 virus-infected mice, sodium cromoglycate alleviated all inflammatory responses and significantly decreased the expression of inflammatory cytokines, including TLR3, IL-6, and TNF- α [125].

A recent study conducted homology modeling to identify all possible therapeutic targets for SARS-CoV-2 and discovered potential drugs by using computational methods. Interestingly, cromolyn sodium was found to be a potential inhibitor of Nsp12, a conserved protein in coronavirus, which is an RNA-dependent RNA polymerase (RdRp). Nsp12-RdRp is considered as a vital enzyme in coronaviruses that modulates replication and transcription processes. Moreover, a previous study demonstrated that Nsp12-RdRp had been used as an important drug target in SARS-CoV and MERS-CoV [126]. Coronaviruses possess ion channels called viroporins that play an important role in regulating virus replication and serving as a potential drug target, in particular chloride and calcium ion channels [127,128]. Cromolyn sodium has a direct effect on those channels [129,130], so targeting ion channels is of great importance to impede the virus life cycle [128]. Cromolyn has a well-studied pharmacokinetic profile and has been used for several decades for the treatment of asthma, with a favorable safety

profile in children and pregnant women [131]. Clinically, the inhalation route was shown to be the most effective route to achieve desirable systemic bioavailability [132]. It is important to note that cromolyn sodium was shown to be ineffective in the treatment of acute attacks of asthma. Indeed, it functions exclusively as a prophylactic agent in the management of chronic symptoms with a low incidence of adverse effects [130]. This suggests that it would be more optimum as a protective agent against ARDS associated with COVID-19 that could be used at earlier stages of the disease rather than in progressive states.

Ketotifen as well reduces inflammation in response to virus infection, including H5N1 virus-infected mice [121], and the inflammation associated with infectious Newcastle disease virus (NDV) [133]. In H5N1 infection, it reduces lung lesions and apoptosis and it is effective at the early stages of H5N1 infection [121]. Quercetin and luteolin are structurally related; after screening several compounds, luteolin was found to significantly inhibit SARS-CoV activities *in vitro*, targeting the entry process of the virus into host cells. Similar results were validated in a separate experiment in the case of quercetin [134]. In addition, quercetin inhibits serine proteases [135], and its derivatives were found to inhibit SARS-CoV 3C-like protease (3CL(pro)), which plays a critical role in viral infectivity [136].

Taken together, the use of MC stabilizers at early-stage infection should be taken into consideration, as that may attenuate SARS-CoV-2 infection and reduce its pulmonary complications, ARDS, and cytokine storm. In terms of ongoing clinical trials, no current studies are conducted to examine the utilization of MC stabilizers in SARS-CoV-2 except one study mentioned in Table 2. Consideration of using MC stabilizers prophylactically and synergistically with other anti-inflammatory agents may also be feasible.

3.5.2. Inhibitors of mast cell mediators

Products of mast cell degranulation are known for their dominant role in triggering an inflammatory reaction and cytokine storm in severe cases, which results in ARDS that facilitates the process of disease exacerbation and multiple-organ failure [137]. Targeting those mediators is of great importance; many drugs are available to target and block the activity of specific MC mediators, including TNF-α, leukotrienes, and mast cell proteases.

TNF is released in the acute phase of inflammation. It is a pyrogen cytokine associated with many autoimmune inflammatory diseases, such as rheumatoid arthritis [138], where the level of IL-6 is mainly induced by TNF-α. Despite the presence of many inflammatory cytokines, the blockage of TNF alone was shown to be highly effective in many diseases [139,140]. TNF can cause TNF-dependent cytokine cascade in rheumatoid arthritis [141]. In SARS-CoV, TNF-α promotes virus pathogenesis and preassembly [142]. TNF inhibitors like etanercept, preferred over infliximab, have a short half-life, a well-recorded safety profile, and are less immunogenic. Lastly, the time of administering TNF inhibitors is critical due to the potential reduction of immune-mediated pulmonary injury [143].

Leukotriene mediators released from mast cells, basophils, and eosinophils [144] play a significant role in the pathogenesis of asthma. Two types of leukotrienes are cysteinyl leukotrienes (CysLTs) and leukotriene B4 (LTB4). CysLTs cause smooth muscle contraction, swelling, and edema in the airways' wall, while LTB4 is considered a potent chemoattractant and activator for neutrophils and eosinophils [145]. Targeting leukotriene mediators is achieved in two ways. One is through leukotriene synthesis inhibitors by targeting 5-lipoxygenase enzyme, such as zileuton, and the other is by leukotriene-receptor antagonists that block CysLT1 receptor on target cells, such as montelukast and zafirlukast [146]. In SARS-CoV-infected monocytic cells 24 h post-infection, the gene expression level of leukotriene A4 was upregulated [147]. It's worth mentioning that montelukast might have antiviral activity, as it targets SARS-CoV-2 3CL protease and fits properly with stable conformation [126]. Indeed, montelukast exhibited antiviral activity against a wide range of viruses, including Zika virus (ZIKV), DENV-2, and yellow fever virus (YFV) [148]. The use of montelukast, a potent well-known leukotriene modifier in SARS-CoV-2, may control and prevent the stage of cytokine storm with potential antiviral activity as well.

Lastly, mast cells express a number of cell-specific proteases, including tryptase [149]. Its inhibitor, camostat mesylate, was found to prevent SARS-CoV entry into the cells by targeting the transmembrane protease serine 2 (TMPRSS2) and blocking the spread and pathogenesis of the virus [150]. SARS-CoV-2 as well depends on TMPRSS2 for S protein priming, and camostat mesylate partially blocked SARS-CoV-2 S-protein driven entry into the lung [97]. These findings support the role of mast cell-targeting drugs in suppressing excessive uncontrolled inflammation in response to highly virulent viral infections, such as SARS-CoV-2, which encourages further examination of their role, especially in the case of asthmatic exacerbations during SARS-CoV-2 infection. Few clinical trials are ongoing right now to investigate their use (Table 2). Results from those trials could open new insight into SARS-CoV-2 treatment.

3.6. Corticosteroids

Corticosteroids can effectively reduce the inflammation associated with various conditions [151]. They bind to cytoplasmic corticosteroid receptors, which translocate to the nucleus and reduce the activity of pro-inflammatory transcription factors, such as NF-kB and activator protein-1 (AP-1) [152]. The activation of corticosteroid receptors also regulates the transcription of anti-inflammatory genes [152]. As a result, many inflammatory mediators involved in the cytokine storm are reduced upon corticosteroid treatment. However, the use of these agents in controlling the inflammation associated with COVID-19 has been controversial [153,154]. One of the reasons hindering their utilization in viral infections is their immunosuppressive behavior [155]. Corticosteroids can influence the function of many immune cells. For example, they antagonize the differentiation of macrophages, inhibit the activation of T cells, reduce the number of circulating B cells and suppress the activity of dendritic cells [155].

Corticosteroids were administered in the previous SARS outbreak. However, the clinical data for their use was conflicting with no clear answer to whether they enhance or deteriorate the condition of the patients [156,157]. There was evidence that the early administration of corticosteroids to SARS patients delayed viral clearance and resulted in higher plasma viral load [156]. On the other hand, it was also shown that their administration in critically ill SARS patients decreased mortality rates [157]. Because of the inconclusive evidence with their use, the treatment guidelines released by the WHO on January 28, 2020, recommended against administering corticosteroids to COVID-19 patients unless indicated for other conditions [154]. Nevertheless, emerging evidence revealed that dexamethasone, a widely available and inexpensive corticosteroid, is associated with reduced mortality in critically ill COVID-19 patients [158]. Based on these reports, the WHO welcomed the preliminary data about dexamethasone use on June 16, 2020 [159].

A recent study revealed that early administration of the corticosteroid methylprednisolone to hospitalized COVID-19 patients enhanced the clinical outcome [160]. In this study, 81 patients received standard of care therapy, while 132 patients received early treatment with methylprednisolone (0.5 to 1 mg/kg/day divided into two intravenous doses for three days). By the end of the study, the methylprednisolone group had fewer patients needing transfer from the general medical unit to ICU, fewer patients needed mechanical ventilation, and the length of hospital stay and mortality were both reduced [160]. These beneficial effects might result from reducing the excessive inflammatory responses of COVID-19 [160].

Another study showed that early administration of dexamethasone to patients suffering from ARDS could reduce the duration of mechanical ventilation and mortality [161]. With the hope that the anti-

inflammatory and antifibrotic effects of dexamethasone could mitigate the pulmonary and systemic damage associated with ARDS, the researchers conducted a randomized, multicenter, controlled trial, consisting of 277 patients to compare the administration of dexamethasone to conventional ARDS treatment (NCT01731795). Patients in the dexamethasone group were administered an intravenous dose of 20 mg once daily from day 1 to day 5, and then the dose was reduced to 10 mg once daily from day 6 to day 10 [161]. It was revealed that patients in the dexamethasone group needed less duration of mechanical ventilation, and their overall mortality was reduced compared to patients receiving routine ARDS intensive care [161].

Interesting results supporting the use of dexamethasone in severe cases of COVID-19 is gaining a lot of attention. The preliminary results of a large randomized, controlled, open-label trial conducted in the United Kingdom are in favor of dexamethasone use [158]. This trial investigated a range of possible therapies in hospitalized COVID-19 patients. Dexamethasone arm constituted 2104 patients receiving 6 mg dexamethasone (oral or intravenous) once daily for up to 10 days, and 4321 patients receiving standard care [158]. By the end of 28 days, dexamethasone's effect was most significant in patients receiving respiratory support [158]. It reduced the mortality by 35% in patients receiving invasive mechanical ventilation and by 20% in patients receiving oxygen support only without invasive mechanical ventilation [158]. All patients allocated to the dexamethasone group had a shorter duration of hospitalization compared to patients receiving standard care, and their probability of discharge within 28 days was higher [158]. Despite the remarkable clinical improvement of the patients that were receiving respiratory support, dexamethasone did not show benefit in those who were independently ventilating [158]. A possible explanation for this could be that, at the later stages, where COVID-19 is severely affecting the lung function and restricting the patient's respiration, the disease is mostly driven by immunoinflammatory reactions that can be attenuated by the use of corticosteroids [158]. The replication of the active virus at this stage might be playing a secondary role in the disease [158]. Therefore, controlling the inflammation at this later stage with dexamethasone holds a great chance to enhance the treatment outcome of COVID-19 patients.

In summary, the outcome of administering corticosteroids seems to largely depend on the clinical status of the patient, the dose administered, and the time at which it is administered. It is also critical to determine the phase of the disease at which the viral pathogenicity is most influential, compared to the phase at which the host inflammatory responses dominate the pathology. These points should be kept in consideration to optimize the use of corticosteroids, such as dexamethasone in COVID-19, especially that this drug is a widely available inexpensive option, with an advantage of a long duration of action permitting once-daily dosing [162]. Optimizing the use of dexamethasone might achieve therapeutic improvement in COVID-19 and reduce the burden on healthcare when used in the right patient, at the right dose and at the right time.

3.7. Other agents

Other than the drugs mentioned above, several other therapeutic agents were recommended to be used in the cytokine storm phase of COVID-19. Intravenous immunoglobulin (IVIG) therapy involves a concentrated preparation of globulins prepared from pooled plasma of thousands of healthy blood donors. It has an established role in the management of several autoimmune disorders and hyperinflammatory states and proved beneficial in treating cytokine storm associated with SARS and H1N1 influenza infections [163]. Its effects on COVID-19 associated ARDS are currently being assessed in phase 3 clinical trial (NCT04350580).

Despite the controversies surrounding the use of angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) in COVID-19 patients, some are recommending its use in the subset of COVID-19 patients that present with ARDS. The rationale behind this is that even though these agents upregulate the expression of ACE-2 on cells, this could have a protective effect in patients with lung injury arising from cytokine storm. The RAS system also plays a role in activating pro-inflammatory cytokines, so interfering with this system could potentially benefit a subpopulation of patients with severe COVID-19 [35]. Till the moment, there is no consensus on whether ACEI and ARBS are useful or harmful, but many observational studies are taking place to better clarify their effects on COVID-19 patients.

Another class of agents that were proposed is α1-adrenergic receptor (α1-AR) antagonist, such as prazosin [164]. A previous study elucidated the role of α1-AR signaling in enhancing the level of pro-inflammatory cytokines like IL-6 and demonstrated how the administration of prazosin could provide protection against cytokine release syndrome by attenuating cytokines responses [165]. As prazosin is a well-tolerated drug, it could bring many benefits to the clinics if proven effective. For this purpose, a phase 2 clinical trial is being run to compare outcomes of COVID-19 patients receiving prazosin with patients receiving standard therapy (NCT04365257).

There have been speculations about the role of vitamin D in reducing the mortality rates due to COVID-19, which could be attributed to its immunomodulatory properties [166]. A study done on HIV patients revealed a significant association between vitamin D deficiency and increased levels of IL-6 [167]. Similarly, a preprint reported a potential association between vitamin D deficiency and elevated CRP levels in COVID-19 patients, which is one of the hallmarks of cytokine storm [168]. These data suggest that vitamin D supplementation could possibly be used as a cheaper and more available alternative to IL-6 inhibitors in preventing COVID-19 associated cytokine storm. The role of vitamin D levels in COVID-19 is currently being investigated in several clinical trials.

4. Conclusion

With the exponential rise in COVID-19 cases worldwide, there is an urgent need for effective treatments that would minimize the number of mortalities due to the disease. Emerging evidence points to cytokine storm as the main culprit in COVID-19 progression and the development of complications in a certain subset of patients, such as ARDS and multiorgan failure that could lead to fatal consequences in many individuals [4,41]. Cytokine storm is a result of the overproduction of pro-inflammatory cytokines, thus interfering with the production and signaling of these cytokines seems to be a very promising approach for treating severe cases of COVID-19. In this paper, we shed light on some therapeutic agents that have established roles in several autoimmune and inflammatory conditions, such as IL-1 inhibitors, IL-6 inhibitors, JAK inhibitors, chloroquine, mast cell inhibitors, and corticosteroids. We highlighted the potential some of these agents have based on previous experiences using these agents with other infectious and inflammatory diseases, as well as the successes some of these agents have shown in small trials on COVID-19 patients. The accumulating data point to the benefits that these agents could bring in terms of improving patients' conditions and increasing the survival rates in critically ill patients with complications due to the cytokine storm [47,52,72,82,158]. This data, however, is still limited, and more evidence needs to be gathered before clinicians could come up with conclusions regarding the use of these therapeutics in COVID-19 patients. There are also several questions that need to be answered, such as which subset of patients would benefit the most of these drugs, and whether screening patients for inflammatory markers before drug administration could aid in tailoring therapeutic regimens to patients. It is also important to know at which stage of the disease would these agents be the most beneficial. For example, could they be used as a prophylactic therapy to prevent cytokine storm at early stages of the disease or would their immunosuppressive properties delay viral clearance and also give a chance for opportunistic pathogens to arise. Results from

controlled clinical trials will provide us with more knowledge about the actual value that these drugs would bring to COVID-19 patients. They would also give us more insight into which immunomodulatory agents would be the most optimum for COVID-19 patients, and whether combining these agents with antiviral therapy would have a synergistic effect. It would also be interesting to know how effective corticosteroids and mast cell stabilizers are in attenuating cytokine storm in comparison to other agents. As the cost and availability of some of the other agents could hinder their use in clinics in many countries. On the other hand, corticosteroids like dexamethasone, as well as mast cell inhibitors, would provide a major advantage to clinicians if proven to be as effective as drugs like cytokine blockers due to their accessibility by the vast majority of the population. Answering these questions will not only help us in treating the current COVID-19 pandemic, but it will also guide us in managing similar infectious diseases in the future.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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