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## Review Article

# Anti-inflammatory and immune therapy in severe coronavirus disease 2019 (COVID-19) patients: An update

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## ABSTRACT

In March 2020, when coronavirus disease 2019 (COVID-19) was just beginning to spread around the world, we presented the potential benefits and controversies of anti-inflammatory therapy in COVID-19 patients based on the limited experience and proposed some types of anti-inflammatory drugs with potential therapeutic value, while without evidence-based data. In the past one more year, many clinical trials or real-world studies have been performed, either confirm or deny the efficacy of certain anti-inflammatory drugs in the treatment of COVID-19. In this review we summarize the progress of anti-inflammatory and immune therapy in COVID-19, including glucocorticoids, IL-6 antagonist, IL-1 inhibitor, kinase inhibitors, non-steroidal anti-inflammatory drugs and chloroquine/hydroxychloroquine.

## 1. Introduction

Two years ago, when the pandemic outbreak of coronavirus disease 2019 (COVID-19) was just beginning to spread around the world, we presented the potential benefits and controversies of anti-inflammatory therapy in COVID-19 patients based on the limited experience and proposed some types of anti-inflammatory drugs with potential therapeutic value [1]. At that time, these drugs were lack of support of evidence-based medicine. One more year later, there have been many clinical trials or real-world studies either confirm or deny the efficacy of some kinds of anti-inflammatory drugs in the treatment of COVID-19. In this review we will summarize the progress of anti-inflammatory and immune therapy in COVID-19.

Many risk factors have been identified for COVID-19 to progress into a severe and critical stage, among which the imbalance of the immune system is one of the important reasons.

A number of studies and meta-analysis from different countries have

reported many risk factors for COVID-19 to develop into a severe and critical stage, including old age, male gender, smoking, comorbidities (such as hypertension, diabetes, obesity, chronic lung disease, heart, liver and kidney disease and tumor), systemic or local immunodeficiency, and pregnancy. Laboratory parameters indicating deterioration include lymphopenia, significant increase in hypersensitive C-reactive protein (CRP), serum ferritin, and pro-inflammatory cytokines such as IL-6 and IL-1 $\beta$ , as well as increase in aspartate aminotransferase, lactate dehydrogenase, D-dimer and Krebs von den Lungen-6 (KL-6) and the activation of coagulation system [2–5].

The state of the body's immune system has important impact on the progression of COVID-19 to a severe and critical stage. Underlying immune states or immune-related treatments also have certain effects on the outcome of COVID-19. Surveys in Chinese Hubei Province showed the risk of COVID-19 infection in rheumatic patients was 2.68 times higher than that in non-rheumatic patients [6], and respiratory failure was more common in rheumatic patients infected with COVID-19 [7]. A

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study including 9 case series found that different anti-rheumatic medicines or biological agents for patients with autoimmune diseases had different influence on the course of the COVID-19. For example, patients treated with hydroxychloroquine or tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) inhibitors had a relatively mild disease, while patients treated with rituximab or interleukin-17 (IL-17) monoclonal antibodies had a relatively severer disease [8]. In addition, another review [9] summarized the clinical data of COVID-19 patients with pre-existing compromised immune systems, which included 36 studies covering 126 patients with different diseases. These patients included 10 cases of congenital immunoglobulin deficiency, such as common variant immunodeficiency (CVID), X-linked agammaglobulinemia due to loss-of-function mutations in the bruton tyrosine kinase (BTK), and 116 cases of acquired immunosuppression, who had been using immunosuppressant for a long time after heart, liver and kidney transplantation. The results showed that organ transplant recipients with COVID-19 had a higher mortality rate overall, which increased significantly with age, comorbidities, and complications. The mortality rate of kidney transplant recipients with COVID-19 was 0% for the <49-year age group; 20.8% for the 50–59-year age group, 12.5% for the 60–69-year age group, and up to 47.1% for the >70-year age group.

Cytokine storm is confirmed to be one of the important reasons for the worsening of COVID-19 patients. Several studies have found significant increase in cytokines in COVID-19 patients' serum, including IL-1, IL-1RA, IL-6, IL-7, IL-8, IL-9, IL-10, granulocyte-colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), chemokine family (CXCL10, CCL2, CCL3), interferon- $\gamma$  (IFN- $\gamma$ ), TNF $\alpha$  and vascular endothelial growth factor (VEGF) [10–12], some of which were more significant in severe patients, such as IL-6, IL-10, IP-10, MCP-3 and macrophage inflammatory protein-1 (MIP-1) [10,13]. Moreover, soluble IL-2 receptor (sCD25) was also significantly increased in most severe COVID-19 patients [11]. Elevated levels of ferritin and other inflammatory factors in peripheral blood also suggested that the activation of macrophage might be highly correlated with disease progression [11].

The IL-6 released by activated macrophages is key to initiating cytokine storms [14,15]. The increase of IL-6 leads to amplification of a series of inflammatory cascades. IL-6 can activate Th17 cells, CD8 + cytotoxic T cells and B cells, and reduce the killing effect of NK cells. In addition, IL-6 can induce the expressions of VEGF, MCP-1 and IL-8 leading to increase permeability of vascular and promote monocyte chemotaxis. Meanwhile, IL-6 can promote production of CRP, ferritin and complement. The above mechanisms can partially explain the key pathophysiological manifestations of severe COVID-19, including acute respiratory distress syndrome (ARDS), hypotension, and disseminated intravascular coagulation [10,11,16]. Therefore, cytokine storm is considered to be one of the important reasons for the development of COVID-19 to critical disease. Many clinical trials on anti-inflammatory cytokine therapy are under way, and some are completed.

However, there are still many problems to be solved about the guiding significance of cytokine storm in treatment of COVID-19. In previously published clinical studies about ARDS caused by other reasons, the median level of IL-6 in peripheral blood of patients was approximately 10 to 200 times than that in severe COVID-19 patients [17]. In addition, in patients with severe COVID-19, it is difficult to distinguish between protective inflammation (clearance of the pathogen) and pathogenic inflammation (to attack the body). More studies are needed to investigate the role of inflammatory cytokine storms in the process of lung injury and multi-system injury in COVID-19 patients, so as to further verify the significance of targeted inflammatory therapy.

## 2. Anti-inflammatory and immune therapy in patients with COVID-19

Given that patients with severe COVID-19 may have various immune imbalances, a variety of immunomodulatory drugs have been applied in

severe patients, which mainly includes the following categories: 1) drugs mainly to inhibit systemic or local excessive immune and inflammatory response (cytokine storm), such as glucocorticoids, inflammatory cytokine inhibitors, kinase inhibitors, and non-steroidal anti-inflammatory drugs; 2) Blood products, such as plasma from recovered COVID-19 patients, gamma globulin, mesenchymal stem cells; 3) biological agents with the ability to enhance the antiviral immune response, such as interferon; 4) drugs may have both antiviral and immunomodulatory ability, such as hydroxychloroquine; 5) treatment which can directly remove inflammatory factors and toxins from patients' body, such as blood purification. Some of these clinical trials have been completed, which support or oppose their applications, but more clinical studies are still in progress.

### 2.1. Glucocorticoids

Glucocorticoids have powerful anti-inflammatory action, which can inhibit inflammation caused by multiple causes. Glucocorticoids have been used in certain condition of viral pneumonia, such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and influenza. Although some clinical trials have confirmed that glucocorticoids have a good effect on ARDS and sepsis [18–20], it is still with controversy [21,22]. To date, about 100 studies on glucocorticoids with treatment of COVID-19 have been registered in the Clinical Trial website from countries around the world.

A large, multicenter, open-label Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial was conducted in the UK, which included clinically suspected or laboratory confirmed COVID-19 patients without history of significant risk for participating in the study upon evaluation, and excluded patients with clear indications for glucocorticoids [23]. A total of 2104 patients were randomized to receive usual care combined with dexamethasone 6 mg once per day for ten days and 4321 patients were randomized to usual care alone. The 28-day mortality in the dexamethasone group (482 deaths, 22.9%) was significantly lower than in the usual care group (1,110 deaths, 25.7%) (RR 0.83, 95% CI 0.75–0.93,  $P < 0.0001$ ). Dexamethasone showed no significant benefit in patients who did not require respiratory support at the time of enrollment, with 28-day mortality higher than the usual care (17.8% vs 14.0%, RR 1.19, 95% CI 0.91–1.55); while for patients who required oxygen at beginning of the study, 28-day mortality in the dexamethasone group was lower than that in the usual care group (23.3% vs 26.2%, RR 0.82, 95%CI 0.72–0.94); 28-day mortality in patients who required invasive mechanical ventilation was lower in the dexamethasone group than in the usual care group (29.3% vs 41.4%, RR 0.64, 95% CI 0.51–0.81). In addition, dexamethasone was observed to reduce 28-day mortality in patients with symptoms longer than 7 days. The RECOVERY study received great international attention and the regimen has been put into clinical use quickly in the UK.

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group conducted a prospective meta-analysis, pooled data from 7 randomized clinical trials (RCT) to evaluate the efficacy of corticosteroids in 1703 critically ill patients with COVID-19 (including 1007 patients in RECOVERY study) [24]. 71% of patients were male and the median age was 60 years old, 1459 patients received invasive mechanical ventilation. There were 425 deaths among 1,025 patients randomized to usual care or placebo and 222 deaths among 678 patients randomized to glucocorticoids, suggesting that 28-day all-cause mortality of critically ill COVID-19 patients treated with glucocorticoids was lower than those treated with usual care or placebo (OR 0.66, 95% CI 0.53–0.82,  $P < 0.001$ ). The study further analyzed the effect of glucocorticoids dose on mortality. The glucocorticoids dose was divided into high and low based on the cutoffs of 1 mg/kg/d of methylprednisolone, 15 mg/d of dexamethasone, 400 mg/d of hydrocortisone [19]. 28-day all-cause mortality in high dose group was lower than those with usual care or placebo (OR 0.83, 95% CI 0.53–1.29,  $P = 0.46$ ); so was low dose glucocorticoids (OR 0.61, 95% CI 0.48–0.78,  $P < 0.001$ ). The

analysis showed that 28-day all-cause mortality was lower in patients with glucocorticoids than with usual care or placebo irrespective of receiving invasive mechanical ventilation (OR 0.69, 95% CI 0.55–0.86 for patients with invasive mechanical ventilation; OR 0.41, 95% CI 0.19–0.88 for patients without invasive mechanical ventilation). The overall safety of glucocorticoids therapy was good.

A systematic review and network meta-analysis of COVID-19 drugs [25] showed that mortality was lower in patients with glucocorticoids treatment than usual care (OR 0.87, 95% CI 0.77–0.98). In addition, glucocorticoids reduced the risk of requiring mechanical ventilation in patients with COVID-19 (OR 0.83, 95% CI 0.58–0.92) and shortened the length of hospitalization (mean difference – 0.99 days, –1.36 to –0.64 days).

Another systematic review and meta-analysis to evaluate the efficacy and safety of glucocorticoids in patients with COVID-19 included 37 retrospective studies, 5 RCTs, and 2 historical controlled studies with a total of 20,197 patients (median age 34–75 years) [26]. Results showed that for patients with moderate to severe respiratory failure, mortality was significantly reduced in glucocorticoids group (OR 0.72, 95% CI 0.57–0.87). Nasopharyngeal swabs were collected regularly for reverse transcription-polymerase chain reaction (RT-PCR) in 13 trials. As for the viral negative-transforming time, 9 trials showed prolonged in the glucocorticoid group, 2 trials showed prolonged in the usual care group, and 2 trials showed equal in 2 groups. 6 studies reported longer hospital stays in the glucocorticoid group and 5 reported longer stays in the usual care group, and 1 showed no difference in the 2 groups. 14 studies reported that glucocorticoid reduced the number of patients or the time of requiring mechanical ventilation. Of the 6 studies that reported infection, only 1 showed a lower rate of secondary infection in the glucocorticoid group [27], while others showed a higher rate in the glucocorticoid group.

U.K. Chief medical officers [28], World Health Organization (WHO) [29], and National Institutes of Health (NIH) [30] updated guidelines one after another to recommend glucocorticoids for treatment of critically ill patients with COVID-19. However, it should be emphasized that glucocorticoids should be treated with caution, with strict indications, and close monitoring of side effects. At present, more medical evidence is still needed to demonstrate the rational application of glucocorticoids, including types of glucocorticoids, dosage, course of treatment, timing of administration and combination of drug.

## 2.2. Interleukin 6 (IL-6) inhibitors

Current evidence supports that early use of IL-6 receptor monoclonal antibody (tocilizumab) is beneficial for critically ill patients.

As mentioned above, serum IL-6 level is associated with the severity of COVID-19. The increasing level of IL-6 is predictive of the need for mechanical ventilation [31,32]. Therefore, it is speculated that blocking the action of IL-6 may alter the course of the disease. A number of retrospective studies have suggested that tocilizumab might bring clinical improvement and survival benefit to patients with COVID-19, but the bias might exist. For the first time, a team from China retrospectively reviewed 21 patients with severe or critically ill COVID-19 treated with tocilizumab (4–8 mg/kg) and repeated use of tocilizumab if body temperature did not return to normal within 12 h. The results showed that all patients' body temperature returned to normal on the day of treatment, and symptoms and imaging findings improved over the next few days [33]. Since then, most retrospective studies have shown that the use of tocilizumab might reduce the risk of intubation and/or death. A meta-analysis reviewing 1358 patients from 10 different studies found a 12% reduction (95% CI 4.6%–20%) in the risk of death in the tocilizumab group [34]. The largest retrospective study for critically ill patients to date included 3924 ICU patients from 68 US hospitals, 40% of whom required mechanical ventilation support, and 433(11%) received tocilizumab (dose unknown) in the first 2 days of intensive care unit (ICU) admission. After applying inverse probability weighting, it is found that

mortality rate was significantly reduced in the tocilizumab group (HR 0.71, 95% CI 0.56–0.92) [35], and no increase in the risk of secondary infection was observed. In a retrospective study of 154 patients using mechanical ventilation (median follow-up 47 days), the inverse probability weighted model showed a 45% reduction in the risk of death in the tocilizumab group (HR 0.55, 95% CI 0.33–0.90). Meanwhile, the infection rates increased significantly in the tocilizumab group (54% vs. 26%,  $P < 0.001$ ), but the mortality rate did not increase [36].

A randomized, open-label controlled trial (CORIMUNO-TOCI-1) evaluated the efficacy of tocilizumab in patients receiving oxygen treatment (who had not yet received noninvasive or invasive mechanical ventilation). 64 patients in the tocilizumab group (8 mg/kg on Day 1 and Day 3, respectively) had a downward trend in the rate of using mechanical ventilation or death on Day 14, but with no significant difference (24% vs. 36%, HR 0.58, 95% CI 0.33–1.00). In this study, the use of dexamethasone was significantly higher in control group (19%) than in tocilizumab group (9%), which may diminish the efficacy difference between two groups [36]. In another study, tocilizumab (8 mg/kg, followed by a second dose after 12 h) did not reduce the incidence of clinical worsening compared with standard treatment (28.3% vs. 27.0%) [37]. However, 22% of patients in the standard treatment group received tocilizumab as a rescue therapy after clinical worsening, possibly introducing bias in the assessment of efficacy between the two groups [38].

A global, multicenter, randomized, double-blind, controlled, phase III trial (COVACTA) including 452 hospitalized patients with COVID-19 found that tocilizumab reduced the length of hospital stay (median time: 22 vs. 28 days,  $P = 0.037$ ), but did not significantly improve patients' clinical scores at 28 days (seven-category ordinal scale: 1.0 [1.0–1.0] vs. 2.0 [1.0–4.0]) [39]. Later, a double-blind, randomized trial (BACC Bay Tocilizumab Trial) enrolled 243 non-intubated patients with severe COVID-19 but in hyperinflammatory states. There was a downward trend in 28-day intubation rate or mortality in the tocilizumab group, but without statistical significance (10.6% vs. 12.5%, HR 0.83, 95% CI 0.38–1.81) [40]. However, the expected incidence of the end point (30% in the control group and 15% in the tocilizumab group) based on the designed sample size was significantly higher than the final results (12.5% in the control group and 10.6% in the tocilizumab group), so the sample size required for this study may be underestimated. In another randomized, controlled, double-blind trial (EMPACTA) including 389 inpatients with COVID-19 who were not receiving ventilator support, tocilizumab reduced progression to mechanical ventilation or death at 28 days (12.0% vs. 19.3%, HR 0.56, 95% CI 0.33–0.97), but did not reduce the overall mortality at 28 days (10.4% vs. 8.6%) [41].

A Randomized, Embedded, Multifactorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) included critically ill patients with COVID-19 who received high flow oxygen therapy. The median number of organ support-free days was significantly longer in the tocilizumab group (353 patients) compared with the control group (402 patients) (10 [–1–16] vs 0 [–1–15]), and the 21-day mortality was lower (28.0% vs. 35.8%, OR 0.68, 95% CI 0.50–0.91). In this study, all patients received tocilizumab within 24 h after starting organ support in ICU, and the vast majority received dexamethasone [42].

The RECOVERY study mentioned above further evaluated the efficacy of tocilizumab in critically ill patients with COVID-19. The inclusion criteria were the oxygen saturation  $< 92\%$  on air or requiring oxygen therapy and CRP  $\geq 75$  mg/L. Exclusion criteria were similar to described above. 621 (31%) of the 2022 patients randomized to usual standard of care plus tocilizumab group and 729 (35%) of the 2094 patients randomized to usual standard of care alone died within 28 days, with statistically significant difference (RR 0.85, 95% CI 0.76–0.94,  $P = 0.0028$ ). Patients treated with tocilizumab were more likely to be discharged within 28 days (57% vs. 50%, RR 1.22, 95% CI 1.12–1.33,  $P < 0.0001$ ) [43].

In summary, although the benefits and risks of tocilizumab treatment remain to be clarified, available evidences from prospective randomized

controlled studies and retrospective studies on tocilizumab in COVID-19 patients have suggested that tocilizumab might be considered for early use in critically ill patients who require high-flow oxygen treatment or higher levels of respiratory support.

### 2.3. Interleukin 1 (IL-1) inhibitors

Anakinra is a kind of human recombinant IL-1 receptor antagonist, which has been approved for treatment of rheumatoid arthritis, NLRP3 related autoinflammatory disease [44], and severe cytokine release syndrome (CRS) mediated by chimeric antigen receptors-T cells (CAR-T cells) and macrophage activation syndrome/ secondary hemophagocytic lymphohistiocytosis (off-label use). Studies have shown that serum IL-1 $\beta$  is increased in patients with COVID-19 [45]. At present, evidence from some case series has suggested that anakinra might inhibit inflammation and improve prognosis in patients with COVID-19.

A single center case-control study in France included 52 COVID-19 patients treated with anakinra compared with 44 historical patients as control group. Patients in the case group were laboratory confirmed with severe COVID-19 infection or consistent with typical COVID-19 lung infiltration in chest imaging and with severe or aggravated hypoxia. The historical comparison group included patients who met the same criteria and were admitted during the same period of time. Standard treatments for both groups were hydroxychloroquine, azithromycin or parenteral  $\beta$ -lactam antibiotics. Anakinra was given at 100 mg subcutaneously twice daily for 72 h, followed by 100 mg subcutaneously once daily for 7 days. Clinical characteristics were similar between the two groups, but the case group had a lower mean body mass index, a longer duration of symptoms, a higher frequency of use of hydroxychloroquine, and a higher frequency of use of azithromycin. The primary outcome of ICU admission rates due to need of mechanical ventilation or death were 25% (13 patients) and 73% (32 patients) in the case group and control group, respectively (hazard ratio 0.22, 95% CI 0.11–0.41). However, due to the limitations of the study design and unmeasurable confounding factors, the clinical significance of the results is uncertain [46].

A single-center retrospective cohort study in Italy included 29 COVID-19 patients treated with anakinra compared with 16 historical patients as control group. All patients had moderate-to-severe ARDS requiring non-invasive ventilation and hyperinflammation (CRP  $\geq$  100 mg/L or ferritin  $\geq$  900 ng/ml). Anakinra was administered intravenously with a high dose of 5 mg/kg twice daily for a median of 9 days, followed by 100 mg twice daily for 3 consecutive days. Both groups were treated with hydroxychloroquine and lopinavir/ritonavir. The CRP level in the anakinra group decreased in the first few days after treatment, and the 21-day survival rate was higher than that in control group (90% and 56%, respectively,  $P = 0.009$ ). 7 patients (24%) in the high-dose anakinra discontinued treatment due to adverse events (4 of bacteremia, 3 of elevated liver enzymes). A further seven patients received low-dose anakinra, 100 mg twice daily but discontinued treatment after 7 days due to lack of clinical or anti-inflammatory efficacy [47].

Some other case reports or small case series have reported individual evidence of the efficacy and improved prognosis of anakinra in COVID-19 treatment [48–50].

### 2.4. Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are widely used in symptomatic treatment of fever and in anti-inflammatory treatment of rheumatic diseases. It remains controversial regarding usage of NSAIDs in treatment of COVID-19 patients, since little data is available in this area [51].

NSAIDs are not widely used in COVID-19 treatment for various reasons. Firstly, large amount of evidence indicated that the most severe complications of COVID-19 include sepsis, cardiovascular and respiratory failure, especially in the elderly and people with comorbidities [52]. As NSAIDs are associated with cardiovascular adverse events like

myocardial infarction, heart failure and stroke [53,54], this has limited the application of NSAIDs in COVID-19 treatment. Secondly, NSAIDs are associated with renal toxicity [55,56], which may be aggravated in COVID-19 patients who are dehydrated due to fever, gastrointestinal symptoms or dyspnea. Thirdly, it is concerned that NSAIDs might lower the defense mechanism against virus [57,58]. For example, in a large clinical trial, 889 subjects with respiratory infection were randomized into three groups: Paracetamol group, Ibuprofen group, and Combo group in which subjects were given both drugs. The ibuprofen group had higher rate of complications (such as periamygdalitis, sinusitis, meningitis, pneumonia, tympanitis, and progressive or refractory tympanitis) or clinical non-response compared to the Paracetamol group (20% vs. 12%, adjusted HR = 1.67) [59]. Further analysis of this phenomenon indicated that NSAIDs may delay inflammatory responses and relieve infection by inhibiting polymorphonuclear cell recruitment in bacterial pneumonia [60,61]. The most crucial reason, is that studies have found NSAIDs could upregulate angiotensin converting enzyme 2 (ACE2) levels in target human cells [62], and SARS-CoV-2 infects human lungs and other organs by binding ACE2 [63–65], and ACE2 expression is positively related to the risk of coronavirus infections [66], there is possibility that NSAIDs may aggravate COVID-19 patients' conditions.

Therefore, many healthcare organizations, including FDA, EMA and WHO, recommended that although no correlation has been found between NSAIDs and clinical exacerbation of COVID-19, application of NSAIDs in COVID-19 patient should be with cautious [65,67,68]. However, rheumatologists raised different opinions: Firstly, the anti-inflammatory effects of NSAIDs may help prevent lethal cytokine storms in COVID-19, as studies discovered that Ibuprofen could reduce IL-6 in human tissue and sputum. In addition, they suggested patients with chronic inflammatory arthropathy or active arthritis (eg. rheumatoid arthritis or spondyloarthritis) continue their regular NSAIDs unless further evidence is available [69].

### 2.5. Kinase inhibitors

Janus kinase (JAK) inhibitors block JAK signal transducer and activator of transcription (STAT) pathway. JAK-STAT is a cytokine-activating signal transducer pathway which is involved in multiple important biological processes including cell proliferation, differentiation, apoptosis and immunomodulation. JAK inhibitors control immune activation and inflammation in the cells, thus reducing inflammatory cytokines. Presently JAK inhibitors are largely used in the treatment of hematological diseases, rheumatoid arthritis and psoriasis. Theoretically JAK inhibitors could contribute to inhibit hyperinflammation and cytokine storm. Hoang et al. reported that JAK inhibitors can alleviate pulmonary inflammation caused by COVID-19 infection in rhesus monkeys [70]. Many ongoing clinical trials are exploring the role of JAK inhibitors in COVID-19 treatment.

Ruxolitinib is a selective JAK1/JAK2 inhibitor approved in 2011 for myelofibrosis. A prospective, randomized, multi-centered, single-blind study from China evaluated the efficacy of ruxolitinib. Severe COVID-19 patients were randomized 1:1 into two groups, 21 patients with standard of care (SOC) and placebo, 20 patients with SOC and ruxolitinib (5 mg twice a day, until discharged). Baseline treatment included antiviral therapy, intravenous immunoglobulin, and glucocorticoids. The ruxolitinib group had significantly greater improvement in chest CT than in control group (90% vs. 61.9%,  $P = 0.0495$ ) in two weeks and lower mortality rate at Day 28 (0% vs. 14.3%,  $P = 0.223$ ) [71].

Baricitinib is a selective JAK1/JAK2 inhibitor approved in 2019 for rheumatoid arthritis. In a small retrospective study from Europe, 20 severe COVID-19 patients were treated with baricitinib. The result showed that serum cytokine levels dropped quickly, oxygen demand decreased, while the peripheral blood lymphocyte count resumed, and COVID-19 antibody level elevated [72]. Another retrospective study from Europe compared 83 severe COVID-19 patients treated with baricitinib and another 83 baseline-matched controls. Both groups were

treated with hydroxychloroquine, lopinavir/ritonavir, antibiotics, glucocorticoids and low molecular weight heparin. Baricitinib group had significantly lower rate of mortality and mechanical ventilation (16.9% vs. 34.9%,  $P < 0.001$ ). Multivariate cox analysis indicated that baricitinib was an independent factor for improving the prognosis (HR 0.29, 95% CI 0.15–0.58,  $P < 0.001$ ) [73]. A global multi-center, double-blind, randomized phase-III clinical trial (ACTT-2 Study) evaluated the efficacy of add-on therapy with baricitinib on the basis of remdesivir. Among 1033 inpatients of COVID-19 patients (control group) were treated with remdesivir for 14 days. 515 patients (baricitinib group) received remdesivir therapy and baricitinib (4 mg, twice a day) for 14 days. As a result, the treatment group had shorter recovery time than control group (7 days vs. 8 days,  $P = 0.03$ ), and a 30% higher rate of clinical improvement on D15 (OR 1.3, 95% CI 1.0–1.6). Among patients who needed high flow oxygen therapy or non-invasive ventilation, baricitinib group had more significant improve in recovery time (10 days vs. 18 days, RR 1.51, 95% CI 1.10–2.08) [74]. It is noteworthy that 233 patients received glucocorticoids for conditions like adrenocortical insufficiency and septic shock, so it is difficult to ascertain whether adding baricitinib to dexamethasone could further improve prognosis. US FDA has granted emergency license to baricitinib for COVID-19 patients more than 2 years old needing oxygen therapy, mechanical ventilation or extracorporeal membrane oxygenation, but clinicians still need to be cautious with baricitinib, since much remains unknown about the right population and concomitant drugs.

Bruton kinase inhibitors (BTK) is the key kinase in B cell receptor signaling pathway. It plays an important role in regulating B cell development, chemotaxis and adhesion. BTK inhibitors, including ibrutinib, acalabrutinib, and zanubrutinib, have been approved for various types of B cell lymphoma.

In vitro studies and animal studies have shown that BTK inhibitors are potentially effective for COVID-19 treatment through inhibition of macrophage activation and effector B cell functions, as well as alleviating systemic inflammation [75]. However, very limited data have been reported on the clinical application of BTK inhibitors. Only one study including 19 severe COVID-19 patients showed that after adding acalabrutinib to standard therapy, most patients achieved decrease of inflammatory factors including serum C-reactive protein and IL-6 1–3 days, and 72.7% patients stopped oxygen therapy within 10–14 days [76].

In summary, preliminary data showed efficacy of JAK inhibitors in severe COVID-19 patients, but evidence is insufficient regarding efficacy and safety of BTK inhibitors in severe COVID-19 patients. There are many ongoing clinical trials which may provide more information on this issue.

## 2.6. Chloroquine/hydroxychloroquine

At the beginning of COVID-19 pandemic, scientists discovered in vitro studies that Chloroquine (CQ) and Hydroxychloroquine (HCQ) can inhibit glycosylation of ACE2 receptors [77] and block SARS-CoV-2 transfer from primary endosomes to intracellular lysosomes, thus potentially preventing the release of viral genome [78]. In addition, HCQ and azithromycin are both zinc ionophore that could inhibit SARS-CoV-2 replication [79]. CQ and HCQ were once considered highly promising therapies against SARS-CoV-2. Clinical trials were conducted in many countries evaluating CQ and HCQ in COVID-19 treatment, and in some of these studies they were combined with azithromycin.

In March 2020, a single-arm retrospective study was conducted in France [80], in which 20 COVID-19 patients were given HCQ (600 mg/d), 6 of them received azithromycin concurrently, and compared with 16 patients in the control group. In HCQ group, viral load has dropped in 50% of patients on Day 3 ( $P = 0.005$ ), and 60% ( $P = 0.04$ ), 65% ( $P = 0.006$ ), 70% ( $P = 0.001$ ) on D4, D5 and D6 respectively. Therefore, it was believed that HCQ could reduce viral load in COVID-19 patients. In addition, all of the 6 patients who received azithromycin and HCQ had a

decline of viral load on D6 ( $P < 0.001$ ), indicating synergistic effects of combination therapy with azithromycin and HCQ.

However, following studies from US [81–83], UK [84] and Brazil [85,86], including large-scale cohort studies, observational studies, and randomized studies, have reported negative results. For example: In a large retrospective observational study from New York [82], a total of 1376 patient were included. In this study, 811 patients were treated with HCQ, all patients were followed up for 22.5 days (median time). 232 patients died, of whom 66 underwent intubation. 114 received invasive mechanical ventilation, and fortunately survived. No significant advantage was found between HCQ and intubation or death (HR 1.04, 95% CI 0.82–1.32).

The RECOVERY collaborative group randomly distributed 4716 patients into either standard care group or HCQ group in a 2:1 ratio [84]. 28-day mortality rate of HCQ group (26.8%) was not lower than that of the control group (25%) (RR 1.09, 95% CI 0.96–1.23,  $P = 0.18$ ). Moreover, within the subgroup not on invasive ventilation at baseline, likelihood of subsequent intubation or death in HCQ group was higher than control (29.8% vs. 26.5%, RR 1.12, 95% CI 1.01–1.25).

A multi-center, randomized, open-label, controlled study from Brazil [86] also showed HCQ or HCQ/azithromycin combination was unable to improve the prognosis of mild-to-moderate COVID-19 inpatients. Patients treated with HCQ or HCQ/azithromycin combination were not more likely to have prolonged QT intervals and elevated transaminase compared to control.

In summary, no consistent data was generated from large retrospective observational studies regarding the benefits of CQ/HCQ alone or combination with azithromycin to COVID-19 patients. By contrast, many large randomized studies showed no statistically significant difference between adding standalone CQ/HCQ or combination with azithromycin to standard of care and the control group. It is not recommended to use CQ/HCQ alone therapy or combination with azithromycin for COVID-19 treatment.

## 2.7. Other immunological therapies

Apart from the aforementioned anti-inflammatory therapies, various other immunological treatments have been tried during the past year, such as intravenous immunoglobulin (IVIG), COVID-19 convalescent plasma or mesenchymal stem cells (MSCs) therapy, as well as interferon with immune-boosting and antiviral effects.

Studies have shown that high dose immunoglobulins (0.3–0.5 g/kg/d for 3–5 days continuously) in early stage are effective for severe COVID-19 patients [87–89].

Currently, a total of 52 trials have been registered globally on Clinical Trial Website regarding convalescent plasma therapy for COVID-19, of which 8 were completed and no results have been reported yet. Though FDA has granted emergency use authorization to convalescent plasma, evidence-based data supporting its efficacy and correct timing are still insufficient.

MSCs were considered for COVID-19 treatment for their potential effects in immune regulation, inhibition of cytokine storm, reducing pulmonary fibrosis, enhancing self-repair capacity of lung tissues and clearing bacteria [90]. The understanding about usage of MSCs and relevant products in COVID-19 treatment is still preliminary [91,92]. More clinical trials are needed to evaluate its benefits regarding the right population, origins of MSCs, timing and dose protocol.

Interferon is a group of cytokines with antiviral properties. However, studies have shown no efficacy of either interferon- $\alpha$  or interferon- $\beta$  in COVID-19 patients. Moreover, interferon generated significant toxicity and side effects that outweighed its potential benefits [93–95].

In conclusion, during one and half year's global pandemic of COVID-19, doctors and scientists from all over the world have carried out a large number of clinical trials while actively fighting the disease. A lot of important progresses have been made in immune-related treatments and anti-inflammatory therapy. With the widespread application of

vaccination and more effective treatments, the pandemic will be overcome eventually, and severe patients will be more effectively controlled.

## Declaration of Competing Interest

None.

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