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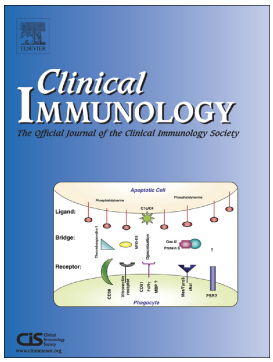


# The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China

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PII: S1521-6616(20)30198-4

DOI: https://doi.org/10.1016/j.clim.2020.108393

Reference: YCLIM 108393

To appear in: *Clinical Immunology*

Received date: 23 March 2020

Accepted date: 24 March 2020

Please cite this article as: W. Zhang, Y. Zhao, F. Zhang, et al., The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China, *Clinical Immunology* (2019), https://doi.org/10.1016/j.clim.2020.108393

# Anti-inflammation treatment of severe coronavirus disease 2019 (COVID-19): from the perspective of clinical immunologists from China

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Abstract: The pandemic outbreak of coronavirus disease 2019 (COVID-19) is rapidly spreading all over the world. Reports from China showed that about 20% of patients developed severe disease, resulting in a fatality of 4%. In the past two months, we clinical immunologists participated in multi-rounds of MDT (multidiscipline team) discussion on the anti-inflammation management of critical ill COVID-19 patients, with our colleagues dispatched from Chinese leading PUMC Hospital to Wuhan to admit and treat the most severe patients. Here, from the perspective of clinical immunologists, we will discuss the clinical and immunological characteristics of severe patients, and summarize the current evidence and share our experience in anti-inflammation treatment, including glucocorticoids, IL-6 antagonist, JAK inhibitors and choloroquine/hydrocholoroquine, of patients with severe COVID-19 that may have an impaired immune system.

Key words: coronavirus disease 2019 (COVID-19); cytokine storm; anti-inflammation treatment

Disclosure: none.

Since the sudden outbreak of coronavirus disease 2019 (COVID-19) in Wu Han City, China caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in just two more months, the epidemic has rapidly spread all over the world. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic. Till March 22, globally, approximately 303,000 confirmed cases, including more than 12,900 deaths in approximately 150 countries. Data from China have indicated that about 20% of patients developed severe disease, older adults, particularly those with serious underlying health conditions, are at higher risk of death than younger ones. A minority of patients presented with respiratory failure, septic shock and multi-organ dysfunction resulting in a fatality of 4%.

In the past two month, we took part in a serial of remote teleconsultation, discussing several critical ill COVID-19 patients in intensive care unit (ICU) and clinical pathological conference (CPC). Here, from the perspective of clinical immunologist and rheumatologists, we would like to discuss and share our experience in the treatment of severe COVID-19.

**Several important features in critical COVID-19 patients:**

From the point of view of rheumatologists, except for respiratory failure, the critical ill COVID-19 patients have common features: 1) sudden deterioration of disease around one to two weeks after onset; 2) much lower level of lymphocytes, especially natural killer (NK) cells in peripheral blood; 3) extremely high inflammatory parameters, including C reactive protein (CRP) and pro-inflammatory cytokines (IL-6, TNFα, IL-8, et al); 4) destroyed immune system revealed by atrophy of spleen and lymph nodes, along with reduced lymphocytes in lymphoid organs; 5) the majority of infiltrated immune cells in lung lesion are monocytes and macrophages, but minimal lymphocytes infiltration; 6) mimicry of vasculitis, hypercoagulability and multiple organs damage.

Based on the above characteristics of COVID-19, we discuss the following points in terms of treatment.

**Inflammatory cytokine storm was very common in patients with severe COVID-19**

Cytokine storm (CS) refers to excessive and uncontrolled release of pro-inflammatory cytokines. Cytokine storm syndrome can be caused by a variety of diseases, including infectious diseases, rheumatic diseases and tumor immunotherapy. Clinically, it commonly presents as systemic inflammation, multiple organ failure, and high inflammatory parameters.

In infectious diseases, CS usually originates from the focal infected area, spreading all over the body through circulation. In coronavirus pneumonia, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), accompanied by rapid virus replication, a large number of inflammatory cell infiltration and CS led to acute lung injury, acute respiratory distress syndrome (ARDS) and death [1, 2]. Accumulating evidence revealed that a part of severe COVID-19 patients have a elevated cytokine profile resembling CS in SARS and MERS. Huang et al. reported the level of inflammatory factors in patients with COVID-19. They measured cytokine levels in 41 inpatients (including 13 ICU patients and 28 non ICU patients), IL-1B, IL-1RA, IL-7, IL-8, IL-9, IL-10, fibroblast growth factor (FGF), granulocyte-macrophage colony stimulating factor (GM-CSF), IFNγ, granulocyte-colony stimulating factor (G-CSF), interferon-γ-inducible protein (IP10), monocyte chemoattractant protein (MCP1), macrophage inflammatory protein 1 alpha (MIP1A) , platelet derived growth factor (PDGF), tumor necrosis factor (TNFα), vascular endothelial growth factor (VEGF) were

increased, among which IL-2, IL-7, IL-10, G-CSF, IP10, MCP1, MIP1A, TNFα were higher in severe patients[3, 4]. Notably, there was not pronounce difference of serum IL-6 level been the ICU and non ICU patients. However, in another retrospective, multicentre cohort study, the same study group reported a significantly elevation of IL-6 level in non-survival group of patients with COVID-19, as compared with that of the survivals [5]. Several other reports also confirmed the elevation of IL-6 in critically ill patients with COVID-19 [6-8].

In severe COVID-19, although patients have lymphcytopenia, the lymphocytes were activated. One study analyzed the lymphocyte subsets and cytokines in 123 patients, all patients had lymphcytopenia, The percentage of CD8 + T cell reduction were 28.43% and 61.9% in mild and severe group respectively, and the NK cell reduction were 34.31% and 47.62% respectively，in mild and severe groups. Also, serum IL-6 levels in severe group were significantly higher than that in mild group [9]. In addition, the expression of HLA-DR in CD4 + and CD8 + cells was increased, CD4 + CCR4 + CCR6 + Th17 cells also increased, and the cytotoxic particles such as perforin and granolysin were highly expressed in CD8 + T cells [10].

Consistent with others, most of severe COVID-19 patients in our ICU ward had persistent very high level of erythematosus sedimentation rate (ESR), CRP, and high level of IL-6,TNFα, IL-1β, IL-8, IL2R, etc, and were associated with ARDS, hypercoagulation and disseminated intravascular coagulation (DIC), manifested as thrombosis, thrombocytopenia, gangrene of extremities. It is possible that CS exacerbates lung damage as well as lead to other fetal complications. Siddiqu and Mehra [11] proposed a 3-stage classification model, recognizing that COVID-19 illness exhibited three grades of increasing severity which corresponded with distinct clinical findings, response to therapy and clinical outcome. A small proportion of COVID-19 patients would transit into the third and most severe stage of illness, which manifested as an extra-pulmonary systemic hyperinflammation syndrome. In this stage, markers of systemic inflammation appeared to be extremely elevated. Therefore, how to block the CS and when to initiate anti-inflammation therapy is critical for reducing death rate of COVID-19.

**The immune system was impaired in critical ill COVID-19 patients**

Lymphocytopenia is one of the most prominent markers of COVID-19, it's also one of the diagnostic criteria for COVID-19 in China [12]. Both T cells and NK cells in patients with COVID-19 were reduced. The degree of reduction was even lower in severe cases the latter had higher leukocytes counts and neutropnil-lymphocyte-ratio (NLR) as well. In some critical ill patients, NK cells were extremely low, or even undetectable. In addition, memory helper T cells and regulatory T cells were obviously decreased in severe cases [13].

More strikingly, the autopsy findings revealed that the secondary lymphoid tissues had been destroyed in COVID-19 patients, which is very unusual from other CS related diseases. Spleen atrophy was observed in all reported cases with decreased numbers of lymphocyte, and significant cell degeneration, focal hemorrhagic necrosis, macrophage proliferation and macrophage phagocytosis were found in spleen. Similarly, lymph node atrophy and the number of lymph nodes decreased, accompanied by necrosis. Immunohistochemical staining showed that CD4+T cells and CD8+T cells were decreased in spleen and lymph nodes [13]. In addition, in the lung with characteristic diffused alveolar damage (DAD), the major infiltrated cells were monocytes and macrophages, moderate multinucleated giant cells, but very few lymphocytes. Most of the

infiltrating lymphocytes were CD4-positive T cells. Importantly, virus inclusion bodies can still be detected in type II alveolar epithelia and macrophages, despite that the PCR test was negative in blood or throat swabs [10, 12, 14]. This finding is consistent with the characteristics of the so called "primary cytokine" storm induced by viral infection which were mainly produced by alveolar macrophages, epithelial cells and endothelial cells, rather than those observed in "secondary cytokine" storm induced by different subsets of activated T lymphocytes in late stage of viral infection or a complication of T cell-engaging therapies [15 16].

There are two possible reasons for the destruction of the immune system in patients with COVID-19, lymphocytes directly invaded by virus or indirectly damaged by CS. As we know that 2019-nCoV infects target cells through ACE2, while there was no ACE2 expression on lymphocytes, we speculate that lymphocytes were probably destroyed by CS.

**Mimicry of vasculitis and thrombosis are prominent features in severe COVID-19 patients.**

Another prominent clinical manifestation in severe COVID-19 patients is endothelium damage. Mimicry of vasculitis could be seen in severe COVID-19 patients. Clinically, many critical ill patients have vasculitis-like manifestations, or even gangrene at their extremities; Pathology examination revealed the blood vessels of alveolar septum were congested and edematous, with modest infiltration of monocytes and lymphocytes within and around blood vessels. Small vessels showed hyperplasia, vessel wall thickening, lumen stenosis, occlusion and focal hemorrhage. Hyaline thrombi of micro-vessels were found in a proportion of severe cases [10, 13, 14]. Intriguingly, some patients were tested positive with high titer antiphospholipid antibodies, including anticardiolipin antibodies and anti-β2 glycoprotein antibodies, and were associated with severe thrombosis (unpublished data). The underlying mechanism of vascular damage may be due to the direct injury of endothelial cells by virus, leading to DIC, anti-phospholipid syndrome (APS) and mimicry of vasculitis. The pathological autoimmune responses involved in the anti-virus immunity are worth to be emphasized.

**Current knowledge of anti-inflammation treatment in COVID-19 patients**

No doubt antiviral and supportive treatments are very important in the treatment of patients with COVID-19. As CS is relatively common in severe case and often leads to the exacerbation, anti-inflammation therapy may help in preventing further injury. As we know, there are a variety of anti-inflammatory medications, including non steroidal anti-inflammatory drugs, glucocorticoids, chloroquine/hydroxychloroquine, immunosuppressants, inflammatory cytokines antagonists (such as IL-6R monoclonal antibodies, TNF inhibitors, IL-1 antagonists, janus kinase inhibitor (JAK) inhibitors, et al. Siddiqu and Mehra suggested that tailored therapy in stage III hinges on the use of immunomodulatory agents to reduce systemic inflammation before it overwhelmingly results in multi-organ dysfunction. In this phase, use of corticosteroids may be justified in concert with the use of cytokine inhibitors such as tocilizumab (IL-6 inhibitor) or anakinra (IL-1 receptor antagonist). Intravenous immune globulin (IVIG) may also play a role in modulating an immune system that is in a hyperinflammatory state. Overall, the prognosis and recovery from this critical stage of illness is poor, and prompt recognition and application of such therapy may have the greatest yield [11, 17].

However, there is dilemma of anti-inflammatory therapy, balancing the risk and benefit ratio is a critical issue. Should we apply anti-inflammation therapy to COVID-19 patients? Which patient should we treat with anti-inflammation regimen, and when to start? What is the treatment duration? Which medication is the best choice? All the above questions are still under intense debate and do not reach a consensus. The main concern is that anti-inflammatory medications, such as corticosteroid, may delay the elimination of virus and increase the risk of secondary infection, especially in those with impaired immune system. Secondly, biological agents targeting on pro-inflammatory cytokines can only inhibit specific inflammatory factor, and thus may not be very effective in curbing the CS in COVID-19 in which other cytokines maybe of significant importance. Thirdly, some anti-inflammation medication such as JAK inhibitors also block INF-a production, which is important in fighting virus, and theoretically may not be suitable for the treatment of inflammatory CS caused by virus as COVID-19. Finally, the time window of anti-inflammatory treatment is very important. According to reports and our observation, severe patients usually underwent abrupt deterioration in 1~2 weeks after onset, and prompt initiation of the anti-inflammatory therapy at this extremely short time window is likely to achieve a favorable treatment response.

**1.** ***Glucocorticoids***

Numerous clinical studies have reported the efficacy of glucocorticoids in the treatment of coronavirus pneumonia (such as SARS and MERS) or influenza pneumonia, but no consensus has been reached. During the SARS epidemic in 2003, glucocorticoid was the main medication of immunomodulatory therapy. Timely usage of glucocorticoid could improve the early fever, promote the absorption of pneumonia and obtain better oxygenation. However, some studies didn't show beneficial effects with glucocorticoid, or even adverse reactions or delayed virus clearance, leading to deterioration of the disease [18-21].

According to international guidelines for management of sepsis and septic shock, if glucocorticoid is to be used, small dosage and short term application should be applied only for patients in whom adequate fluids and vasopressor therapy do not restore hemodynamic stability [22].

At present, systemic glucocorticoids administration was empirically used for severe complications in order to suppress CS manifestations in patients with COVID-19, such as ARDS, acute heart injuries, acute kidney complication, and patients with higher D-dimer levels, et al[3, 23, 24] However, there is no evidence from randomized clinical trials to support glucocorticoids treatment for COVID-19. Chen et al. reported 19 (19%) patients were treated with glucocorticoids for 3–15 days (median 5 [3–7]), and methylprednisolone (1–2 mg/kg per day) are recommended for patients with ARDS, for as short a duration of treatment as possible [25].

The current evidence and our experience indicate that the benefit of the use of glucocorticoids is likely outweighed by adverse effect. Wang et al reported 44.9% patients of COVID-19 were given glucocorticoid therapy, with no effective outcomes observed [26]. Russell et al. reported clinical evidence did not support corticosteroid treatment for COVID-19 lung injury [27]. Due to the lack of evidences, the interim guideline of WHO does not support the use of systemic corticosteroids for the treatment of viral pneumonia and ARDS for suspected COVID-19 cases in 22 February 2020[28]. Therefore, efficacy and associated adverse effects of glucocorticoids in COVID-19 need further elucidated.

**2.** ***Tocilizumab treatment of CS***

Tocilizumab (TCZ) is a recombinant human IL-6 monoclonal antibody, which specifically binds to soluble and membrane-bound IL-6 receptors (IL-6R), thus blocking IL-6 signaling and its mediated inflammatory response. TCZ has been widely used in rheumatic diseases, such as rheumatoid arthritis. On August 30, 2017, TCZ was approved in the United States for severe life-threatening cytokine release syndrome caused by chimeric antigen receptor T-cell (CART) immunotherapy.

Wei Haiming, et al conducted a retrospective study observing the efficacy of tocilizumab in treating severe or critical COVID-19 patients [to be published]. Along with the basic anti-virus treatment, TCZ was applied to 20 patients 400 mg once intravenously. Within a few days, the fever returned to normal and other symptoms improved remarkably. 75.0% had improved oxygenation. The opacity lung lesion on CT scans absorbed in 90.5% patients. In addition, the percentage of peripheral lymphocytes returned to normal in 52.6% patients. Their data suggests TCZ might be an effective treatment in severe patients of COVID-19.

Till now, several clinical trials have been registered on safety and efficacy of tocilizumab in the treatment of severe COVID-19 pneumonia in adult inpatients, including a multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of novel coronary pneumonia (NCP) (ChiCTR2000029765), a single arm open multicenter study on tocilizumab (ChiCTR2000030796), and combination of tocilizumab and other drugs (ChiCTR2000030442 and ChiCTR2000030894).

### 3. *JAK* inhibitors

The receptors of novel coronavirus pneumonia (2019-nCoV), might be ACE2, which is a cell-surface protein widely existed on cells in the heart, kidney, blood vessels, especially lung AT2 alveolar epithelial cells. 2019-nCoV could invade and enter cells through endocytosis. One of the known regulators of endocytosis is the AP2 associated protein kinase 1 (AAK1). AAK1 inhibitors can interrupt the passage of the virus into cells and can be helpful in preventing virus infections. Baricitinib, a JAK inhibitor as well as an AAK1 inhibitor, was suggested a possible candidate for treatment of COVID-19, considering its relative safety and high affinity. Therapeutic dosage with either 2 mg or 4 mg once daily was sufficient to reach the plasma concentration of inhibition [29]. However, as we mentioned above, the biggest concern about JAK inhibitors is that it can inhibit a variety of inflammatory cytokines including INF-a, which plays an important role in curbing virus activity. Further clinical trials and detailed analysis are warranted to confirm their efficacy. To date, there are some registered clinical trials of JAK inhibitor: “Study for safety and efficacy of Jakotinib hydrochloride tablets in the treatment severe and acute exacerbation patients of novel coronavirus pneumonia (COVID-19)” (ChiCTR2000030170); “Severe novel coronavirus pneumonia (COVID-19) patients treated with ruxolitinib in combination with mesenchymal stem cells: a prospective, single blind, randomized controlled clinical trial” (ChiCTR2000029580).

### 4. *Chloroquine and hydroxychloroquine*

Chloroquine (CQ) is an amine acidotropic form of quinine and hydroxychloroquine (HCQ) differs from chloroquine by the presence of a hydroxyl group at the end of the side chain: the *N*-ethyl substituent is β-hydroxylated. For decades, CQ and HCQ are front-line medications for the treatment and prophylaxis of malaria and are also used to treat autoimmune diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).

Previous studies reported that CQ/HCQ possess a broad spectrum of antiviral effects on a variety of viruses as diverse as human immunodeficiency virus (HIV)[30], Marburg virus, Zika virus[31], dengue virus[32], Ebola virus[33], and SARS-CoV-1[34,35], etc. CQ and HCQ can interfere with the binding of viral particles to their cellular cell surface receptor or the pH-dependent endosome-mediated viral entry of enveloped viruses to inhibit the viral cycle [32]. They can also interfere with the post-translational modification of viral proteins or impair the proper maturation of viral protein by pH modulation[36]. In addition, CQ and HCQ can regulate immune system by affecting cell signaling and production of pro-inflammatory cytokines.

Although CQ or HCQ are frequently used for the treatment of rheumatic diseases due to its immunomodulatory and anti-inflammatory effects, the benefit in treating COVID-19 may be mainly attributed to its anti-viral effects. Recently, CQ and HCQ have been shown by several studies to reduce the SARS-CoV-2 viral load and shorten the duration of viremia. Whether their immunomodulatory effect also plays a role in the treatment of COVID-19 still requires further investigation. For coronaviruses, the potential therapeutic benefits of CQ were notably reported for SARS-CoV-1. In vitro, CQ can prevent SARS-CoV-1 from infecting the glycosylation of virus cell surface receptor, ACE2 [30]. A very recent publication of results showed that CQ is highly effective in the control of COVID-19 infection in vitro [37].

Till now, 15 clinical trials have been conducted in China to test the efficacy and safety of CQ or HCQ in the treatment of COVID-19, 8 of which were CQ, 6 were HCQ, and another included both CQ and HCQ [38]. So far, in a clinical trial involving more than 100 patients, the chloroquine phosphate group showed efficacy in reducing the exacerbation of pneumonia, improving lung imaging findings and increasing negative rate of virus nucleic acid test. Given these findings, the Guidelines (version 6) for treatment of COVID-19 recommends chloroquine phosphate is orally administered at a dose of 500 mg (300 mg for chloroquine) for adults, 2 times/ day (no more than 10 days)[39]. "Hydroxychloroquine's therapeutic effect on new coronavirus (COVID-19)" was registered (NO: ChiCTR2000029559). As of February 17, 20 patients have been enrolled in HCQ & basic treatment group. After 1-2 days of HCQ treatment, clinical symptoms in all patients improved. After 5 days of HCQ treatment, 19 patients improved on lung imaging findings. In addition, none of the mild patients had an exacerbation of disease in HCQ group. Regarding to safety, two of them had adverse reactions of mild rash and slight headache, and the adverse reactions disappeared after adjusting the regimen. The results of this clinical trial confirmed the short-term efficacy of HCQ in the treatment of COVID-19, which can effectively improve lung imaging findings, promote a virus-negative conversion, and shorten the disease course. Although the number of cases in HCQ group was relatively small, current data can provide insights for clinicians. The efficacy and safety of HCQ in the treatment of COVID-19 need to be confirmed in further preclinical and clinical trials.

In conclusion, COVID-19 is a viral infectious disease mainly manifested as fever and pneumonia, anti-viral and respiratory supportive therapies are the mainstream of treatments for severe cases. As CS occurs in critical ill patients, which leads to ARDS and multiple organ damage, and even death, anti-inflammation treatment may be applied. However, given the viral nature of the COVID-19 CS, and considering a substantial impairness of host immune system in severe cases, it is critical to balance the risk and benefit ratio before starting anti-inflammation therapy. In addition, a timely anti-inflammation treatment initiated at the right window time is of pivotal importance and should be tailored in individual patient to achieve the most favorable effects.

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Highlights

- The epidemic outbreak of coronavirus disease 2019 (COVID-19) has rapidly spread all over the world.
- Inflammatory cytokine storm was common in patients with severe COVID-19.
- The immune system was impaired in critical ill COVID-19 patients
- A timely anti-inflammation treatment at the right window time is of pivotal importance.