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Mechanism of Glucocorticoid for Treating Severe COVID-19 Patients

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Abstract

Nowadays, novel coronavirus pneumonia, called Coronavirus Disease 2019 (COVID-19) spread rapidly to the whole world and this novel global pandemic has severely threatened the public health. To date, researchers have found that glucocorticoid may be beneficial to decrease the fatality rate in severe COVID-19 patients by a large randomized controlled trial but its specific mechanism is still in debate. This article has put forward two hypotheses about the potential mechanisms of glucocorticoid for treating COVID-19 patients. On the one hand, the progressions of COVID-19 aggravate the injury of lungs and may cause a rare histologic pattern of acute lung injury defined as Acute Fibrinous and Organizing Pneumonia (AFOP). Glucocorticoid may improve the clinical outcomes of severe COVID-19 patients by curing AFOP. On the other hand, the deterioration of COVID-19 can damage to adrenal glands and result in adrenal insufficiency. Thus, the use of glucocorticoids as replacement therapy can modulate the human metabolism and immune response and the clinical conditions of patients will improve.

Keywords: Glucocorticoid; COVID-19; SARS-CoV-2

Background

The Coronavirus Disease 2019 (COVID-19), caused by a novel coronavirus defined as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO), first appeared in the end of 2019 and spread rapidly to the whole world. The most common symptoms of ordinary COVID-19 cases are fever, cough, and fatigue and chest distress, often accompanied by gastrointestinal symptoms or ocular symptoms, such as diarrhea, vomiting, conjunctival congestion and dry eye [1]. The majority of COVID-19 cases usually develop mild to moderate symptoms but some patients may progress to aggravated symptoms and critical illness with hypoxemia and Acute Respiratory Distress Syndrome (ARDS) [2-3]. This emerging pandemic has severely threatened the global public health and still infected more and more people. As of 6th September 2020, there have been 26,763,217 confirmed cases of COVID-19, including 876,616 deaths involved in nearly 200 countries, reported by WHO [4]. Given the urgent public hygiene situation and disastrous global economic damage, therefore, it is important for medical field to explore the proper therapeutic measures for patients with COVID-19.

Nowadays, plenty of drugs were tried to treat COVID-19 patients, such as Hydroxychloroquine (HCQ)/Chloroquine (CQ), Remdesivir, interferon, glucocorticoid, inhibitors of Interlukin-6 (IL-6) and Interlukin-1 (IL-1) and the combination of antiviral drugs. Among these therapeutic measures, low-dose glucocorticoid with a short course was considered to use in severe or critical COVID-19 patients with deteriorating status [1]. In fact, glucocorticoid has been used in previous coronavirus pneumonia caused by Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) but the effect of Glucocorticoid (GC) in patients with severe infection or septic shock had no definitive conclusion [5].

Siddiqi et al. had proposed that the infection time course of SARS-CoV-2 can be divided into three phases, including early infection, pulmonary involvement and hyper-inflammation phase. In the early stage of viral infection, viruses invade, multiply and establish in the host. Then the viruses proliferate rapidly in the lungs and cause localized inflammation in the second stage. A few patients may progress into the most severe phase characterized mainly by systemic inflammation and respiratory failure due to hyper-inflammatory response [6]. Thus, the use of glucocorticoids may be reasonable by reducing inflammation and immunosuppression in this phase. The Severe Acute Respiratory Syndrome (SARS) caused by another coronavirus called Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) in 2003 had similar pathogen and clinical presentation.

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Therefore, this article takes a patient with infection of SARS-CoV as example for exploring the potential of glucocorticoids in treating coronavirus pneumonia. At 2nd February 2003, a 21-year-old female patient present respiratory symptoms and she was admitted to Sun Yat-Sen Memorial hospital at 5th February with a diagnosis of SARS. Her clinical condition got worse and her temperature rose to 39.5°C with body ache all over at 8th February. Besides, her pulmonary damage reaches the peak at radiologic images at 11th February and she received oxygen supplement *via* Nasal cannula because her SpO_2 decreased to 92% to 93% in room air (Figure 1). On the same date, she was administered with methylprednisolone 40 mg/d and the treatment was effective (Figure 2). Her temperature returned to normal and her pulmonary lesions began to disappear and she was finally discharged at 24th February (Figure 3). Based on the change of chest X-ray, clinical doctors inferred that glucocorticoids may improve clinical status of patients with infection of coronavirus through reducing excessive inflammation in the late phase of viral infection. Besides, when the course of patients had continued for no less than 7 days, the fever had existed for no less than 120 h and the patients had extensive pulmonary lesions on radiological images characterized predominantly by migratory lesions or lesions involving several lobes (no less than 3 lung lobes) in two lungs without necrosis or cavities, clinical doctors should start glucocorticoids treatment for patients with severe viral infection. The right timing of using glucocorticoids is significant because the human adaptive immune response need certain time to activate. The cellular immunity usually spends 60 h to 72 h to produce enough effector T cells while the production of antibodies by humoral immunity usually needs 5 to 7 days [7-8]. Therefore, too early use of glucocorticoids will inhibit the initiation of normal human immune system. Moreover, the absence of necrosis and cavities in radiological images can exclude the possibility of secondary bacterial and fungal infection and the presence of migratory pulmonary lesions is one of the common radiologic features of cryptogenic organizing pneumonia [9]. Thus, it is justified to use glucocorticoids for patients with severe viral infection when the symptoms persist more than a week with the progression of radiological images and exclusion of secondary bacterial and fungal infection.

However, the clinical effect of glucocorticoid for COVID-19 patients from different studies was heterogenous. A retrospective cohort (n=72 COVID-19 patients, 51 for glucocorticoid group and 21 for control group) by Ni et al. found that there was no significant difference of the median time in achieving negative SARS-CoV-2 result between two groups (P>0.05), and the side effects in GC group, such as transient hyperglycemia, hypokalemia, acne like skin rash and high blood pressure, were more frequent [10]. On the other hand, a multicentric, open-label trial (n=85 COVID-19 patients, 56 for methylprednisolone (MP) and 29 for control) showed that a short course of MP was beneficial to decrease the risk of the composite end point of admission to ICU, NIV or death of severe COVID-19 patients (RR=0.55, 95% CI 0.33 to 0.91, P=0.024) without major adverse reactions [11]. Besides, a multicenter RCT conducted in 176 National Health Service organizations in UK, (n=6425 hospitalized COVID-19 patients, 2,104 received dexamethasone 6 mg/d for up to 10 days and 4,321 only received usual standard care) found dexamethasone could decrease the 28-day mortality among COVID-19 hospitalized patients who need respiratory support, including those receiving invasive mechanical ventilation (29.3% *vs.* 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and those receiving oxygen without invasive mechanical ventilation (23.3% *vs.* 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94), though it may be not beneficial for mild COVID-19 without respiratory support (17.8% *vs.* 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55) [12]. Therefore, taking the benefits and potential harms into consideration and based on the RCT with large sample size, low-dose GC may improve the clinical outcome and reduce fatality rate for severely or critically ill COVID-19 patients. However, it is regretted that few articles tend to explore more potential mechanisms of glucocorticoid. Here, this article will report the potential mechanism of glucocorticoid for treating patients with severe COVID-19.

Glucocorticoid for coronavirus-associated acute fibrinous and organizing pneumonia

The autopsy performed by Wichmann et al. [13] in Germany, including 12 COVID-19 patients, found the major histopathology of the lungs was Diffuse Alveolar Damage (DAD) with hyaline membrane, microvascular thromboembolism and capillary congestion (8/12, 66.7%). The pulmonary post-mortem of COVID-19 cases by Carsana et al. [14] also demonstrated that the main pathophysiological features of the lungs in severe COVID-19 patients were DAD, inflammatory infiltrates and microvascular thrombosis [14]. Besides, these pathophysiological changes of the lungs resulting from the excessive host immune response can also be observed in other severe viral pulmonary infection, such as influenza virus and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) [15-18].

Hanley and his colleagues conducted autopsy among 10 cases with confirmed COVID-19 in UK and 9 of 10 received full post-mortem examinations while the other only received limited autopsy and they reported that all ten patients had DAD, which was the most

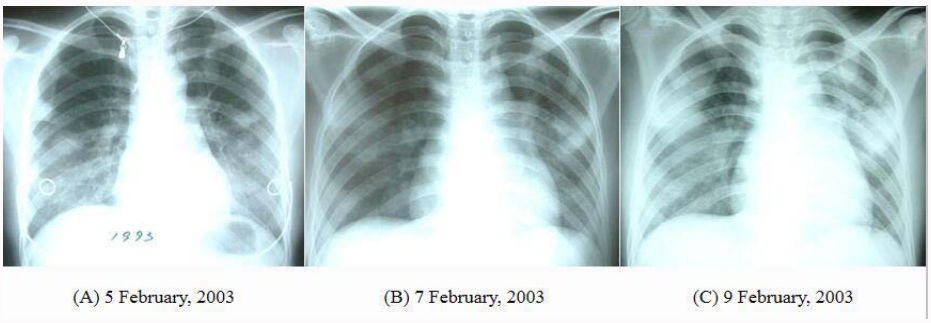


Figure 1: The deterioration of pulmonary lesions on chest X-ray. A) Chest X-ray showed a circular infiltrating shadow in the middle and lower lobe of right lung. B) The lung lesions in bilateral lungs disappeared but a new round ground glass opacity with hazy border appeared in lingual lobe of left lung. C) The infiltrating shadow with high density in the lingual lobe of left lung and the upper lobe of right lung enlarged and patchy opacity appeared in bilateral lower lungs.

consistent histopathological finding of lungs in severe COVID-19 patients. However, in the same study, researchers found that 6 of 10 COVID-19 patients showed purely exudative phase DAD while the other four patients showed a mixture of exudative and organizing DAD and three of four patients with organizing-phase DAD had longer clinical course on ventilators [19]. However, the DAD with organization may mean a different histological pattern of acute lung injury called Acute Fibrinous and Organizing Pneumonia (AFOP), which can result in pulmonary failure and poor prognosis in patients with severe respiratory infection. AFOP was first described by Beasley et al. in 2002 and it is characterized mainly by the presence of organizing intra-alveolar fibrin, with organizing pneumonia, patchy distribution and type 2 pneumocyte hyperplasia [20]. AFOP was firstly suspected as a fibrin variant of DAD without the formation of classic hyaline membrane because both of them had similar etiologic disorders, histologic pattern, and clinical outcome, and it was defined as a rare histologic pattern interstitial pneumonia dominantly characterized by intra-alveolar fibrin deposition and associated organizing pneumonia [21,22].

The incidence of AFOP can be idiopathic or associated with a variety of risk factors, such as autoimmune disease, hematological disorders, drugs, occupational exposure and infection [23]. Viral infection is one of the most common causes of acute lung injury with the histologic manifestation as AFOP. Post-mortem performed among 20 patients with SARS by Hwang et al. showed that the pulmonary histologic features of SARS were DAD and AFOP. Among the 20 decedents, 8 patients showed mainly DAD pattern with the formation of hyaline membrane. Six cases mainly showed AFOP pattern and the remain cases showed the mixture pattern of both DAD and AFOP, which suggested that AFOP was the one of the common pattern of lung injury for patients with SARS. Besides, this study indicated that the extent of lung injury for patients with shorter duration (≤ 14 days' duration) was characterized by acute fibrinous exudates, while those of longer duration (>14 days' duration) showed more organization exudates and pneumocyte hyperplasia [18]. Interestingly, another autopsy of the histopathology of SARS by Franks et al. didn't record AFOP as a finding but the researchers also found four of eight cases, with longer than 10 days' course of disease, showed organizing-phase DAD accompanied by type-2 pneumocyte hyperplasia [24].

Besides, AFOP can also observe in other severe viral respiratory infection, such as H1N1 and Respiratory Syncytial Virus (RSV). Cincotta et al. reported a premature infant with Acute Respiratory Distress Syndrome (ARDS) secondary to the infection of RSV. With the progression of pneumonia, an open lung biopsy was performed and showed nearly 80% of alveolar airspace was occupied by fibrinous balls and organizing tissues with focal RSV-related giant cells. The authors also collected 9 infants dying of ARDS who had received lung biopsies and found that seven cases were demonstrated classic DAD while the remain cases had a mixed AFOP and DAD pattern [25]. Otto et al. reported a female patient with double lungs transplantation and found that she was infected by influenza A/H1N1 soon after transplantation. Despite extracorporeal interventional lung assist implantation, this patient died of acute lung failure soon. Her post-mortem revealed pure AFOP histological pattern with positive influenza A/H1N1 in lung tissues by molecular analysis [26]. Based on the above study, perhaps AFOP is only the late phase of acute lung injury owing to severe viral infection. Therefore, it is reasonable to suppose that DAD predominates in the early phases of acute lung injury and it will change into the organizing phase, until eventually AFOP pattern appears and then predominates [25]. Thus, AFOP, as a histologic pattern of acute lung injury, can occur in patients with severe viral infection, and the lungs with mixture pattern of exudative and organizing DAD in COVID-19 patients found by Hanley et al. may represent the portent of AFOP [19].

Although there have been no definitive therapeutic measures for AFOP, the clinical doctors had tried various treatment according to the heterogeneous clinical presentation and course, such as glucocorticoid, immunosuppression, antibiotics and ventilatory support and GC is the most common used drug for AFOP patients. A retrospective study by Rita et al. with a cohort of 13 cases in Portugal found 10 of 13 (76.9%) patients with AFOP received corticosteroids treatment and 4 of 10 patients (40%) finally gain resolution of disease. However, 6 patients were still alive in this study in the end and it means that 4 of 6 survivals had received glucocorticoid, which suggested that glucocorticoid, was beneficial to the clinical outcome of patients with AFOP. Moreover, another retrospective by Dai et al. including 20 AFOP patients from January 2007 to June 2013 indicated that all patients receiving antibiotic alone had no improvement of clinical remission. However, 18 of 20 patients received glucocorticoid intravenously or orally with the dose from 30 mg to 40 mg prednisone per day soon afterwards and they all felt relieved after steroids treatment within 4.3 ± 2.4 days [27].

The literatures mentioned above suggest that glucocorticoid may relieve the symptoms and improve the clinical outcome for AFOP patients. Table 1 also lists some case reports involving the use of glucocorticoid for hospitalized patients with AFOP (Table 1).

The majority of the studies about AFOP are case reports because pure AFOP is a relative rare disease. Although case reports are considered as the lowest clinical evidence for clinical decisions, researchers can still gain clinical condition and knowledge from them [58]. The case reports in the table has collected the cases receiving glucocorticoid treatment in patients with AFOP and reported the specific usages of glucocorticoid and clinical outcomes of these patients, which can make researchers know more information about AFOP and provide them with optional therapeutic measures and what clinical interventions have succeed or failed in patients with AFOP. Though the definitive therapeutic measures for AFOP is still in debate, the retrospective studies about AFOP and the literatures mentioned above have found that glucocorticoid was the most common and effective treatment to improve the clinical conditions of AFOP patients. Therefore, it is reasonable to infer that glucocorticoid can improve the clinical outcome and decrease the mortality of severe COVID-19 patients by treating the potential AFOP.

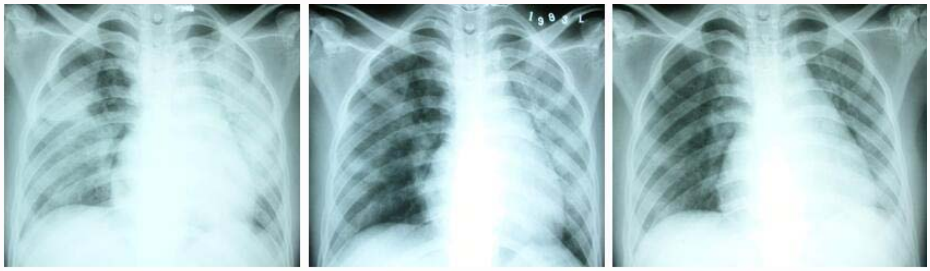
Glucocorticoids as replacement treatment in COVID-19 patients with adrenocortical insufficiency

Except for the DAD or AFOP histologic pattern changes in lungs, patients with severe COVID-19 are susceptible to the lesions in various organs and systems in human body. The autopsy by Hanley et al. found that all nine patients with full post-mortem examinations had at least one thrombotic events in a major organ and they also indicated that acute pancreatitis (2/9, 22%), pericarditis (2/9, 22%) and cirrhosis or bridging hepatic fibrosis (3/9, 33%) could be observed in COVID-19 decedents. Interestingly, the post-mortem examinations also found that 3 of 9 (33%) severe COVID-19 patients showed infarct-type adrenocortical necrosis with patchy distribution and 1 of these 3 patients was found re-endothelializing organizing thrombus

Table 1: The use of glucocorticoid and the clinical outcome in hospitalized patients with AFOP.

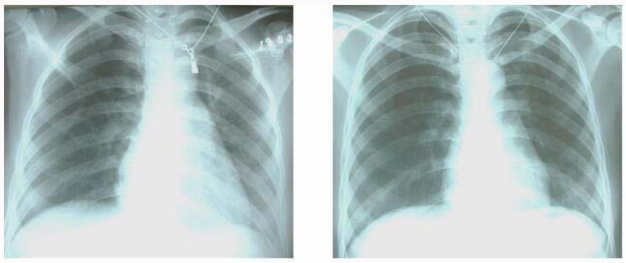
Cases	Reference	The use of glucocorticoid	Clinical Outcome
1	Arnaud et al. [28]	Intravenous steroids and cyclophosphamide (The specific kind and dose of steroids was not mentioned)	Death
2	Xu et al. [29]	Methylprednisolone 500 mg for 3 days and followed by 80 mg for a week	Death
3	Garcia et al. [30]	Methylprednisolone (The dose was not mentioned)	Disease resolution
4	Akhtar et al. [31]	High dose intravenous corticosteroid therapy and followed by prednisolone 40 mg per day	Disease resolution
5	Kim et al. [32]	Methylprednisolone (60 mg/d IV) for 7 days	Disease resolution
6	Kim et al. [32]	Methylprednisolone (60 mg/d IV) for 8 days	Disease resolution
7	Nguyen et al. [33]	Prednisolone (1 mg/kg)	Disease resolution
8	Nguyen et al. [33]	Prednisolone (1 mg/kg)	Disease resolution
9	Ning et al. [34]	Methylprednisolone (40 mg/d IV) for 7 days and followed by methylprednisolone (12 mg/12 h PO) for 7days	Disease resolution
10	Ishiwata et al. [35]	Methylprednisolone (1000 mg/d IV) for 3 days and followed by prednisolone (1 mg/kg PO) for maintainment	Disease resolution
11	Valim et al. [36]	Cyclophosphamide (1 g IV) + methylprednisolone (1 g IV) for 3 days.	Death
12	Chen et al. [37]	Methylprednisolone (80 mg/d IV) for 5 days and followed by methylprednisolone (40mg/d IV) for 3 days. Then the patient received prednisone (40 mg/d PO)	Disease resolution
13	Kuza et al. [38]	Methylprednisolone (60 mg/6h IV) for 2 days, methylprednisolone (125 mg/6 h IV) for 2 days, methylprednisolone (60 mg/6 h IV) for 5 days and followed by prednisone (60 mg/d PO)	Disease resolution
14	Wang et al. [39]	Methylprednisolone (80 mg/d IV) for 2 days, followed by prednisone (75 mg/d PO) for 2 weeks	Disease resolution
15	Hara et al. [40]	Methylprednisolone (1000 mg/d IV) for 3 days, followed by prednisone (0.5 mg/kg/d)	Disease resolution
16	Hara et al. [40]	Methylprednisolone (1000 mg/d IV) for 3 days, followed by prednisone (0.5 mg/kg/d)	Disease resolution
17	Al-Khouzaie et al. [41]	Methylprednisolone (60 mg/6h IV) and followed by prednisone (50 mg/d PO)	Disease resolution
18	Goncalves et al. [42]	Prednisone (1 mg/kg/d; 50 mg/d)	Disease resolution
19	Wang et al. [43]	Methylprednisolone (40 mg/d IV) for 4 days, followed by prednisone (50 mg/d PO) for 21 days	Disease resolution
20	Lu et al. [44]	Methylprednisolone (40 mg/12h IV) and then decreased to 24 mg/d	Disease resolution
21	Lu et al. [44]	Prednisolone (1 mg/kg/d IV) for 10 days, followed by prednisone (40 mg/d PO)	Disease resolution
22	Fasanya et al. [45]	Prednisolone (40 mg/d) and tapered by reduction of 10mg every 2 weeks	Disease resolution
23	Lee et al. [46]	Broad-spectrum antibiotics + methylprednisone pulse therapy (60 mg/d)	Death
24	Kashif et al. [47]	Intravenous immunoglobulin therapy (2 g/kg)+intravenous methylprednisone (The dose of steroids was not mentioned)	Disease resolution
25	Zhao et al. [48]	Methylprednisolone (500 mg/d IV) for 3 days, followed by methylprednisone (40 mg/12 h IV) and antifungal therapy	Disease resolution
26	Yamamoto et al. [49]	Prednisolone (60 mg/d) for treatment and tapering doses (7 mg/d) for maintainment	Disease resolution
27	Shintani et al. [50]	High dose of methylprednisone, followed by prednisone (25 mg/d)	Disease resolution
28	Merrill et al. [51]	Solumedrol (100 mg/d IV) within 6 weeks, followed by prednisone (80 mg/d), which was decreased by 10 mg per week to a maintenance dose of 20 mg	Disease resolution
29	Jamous et al. [52]	High dose of steroids + pentamidine (The dose of steroids was not mentioned)	Disease resolution
30	Gupta et al. [53]	Methylprednisolone (125 mg/6h IV), followed by prednisolone (60 mg/d PO)	Disease resolution
31	Tzouvelekis et al. [54]	High dose of corticosteroid (1 mg/kg) as a monotherapy	Disease resolution
32	Guimaraes et al. [55]	Prednisolone (1 mg/kg/d) for treatment and tapering doses for maintainment	Disease resolution
33	Perry et al. [56]	Intravenous methylprednisolone for 5 days and followed by prednisolone (30 mg/d) for nearly 18 months	Disease resolution
34	Simmons et al. [57]	Methylprednisolone (250 mg/6h IV)+tacrolimus+etanercept (25 mg SC twice weekly)	Disease resolution

in small adrenal vessels, which suggested that severe COVID-19 may cause damage to adrenal cortex and result in adrenal insufficiency [19]. Heidarpour et al. had reported a 69-year-old male patient with COVID-19 and found that the patient presented vasopressor-resistant hypotension and was diagnosed as acute adrenal insufficiency with the deterioration of COVID-19 [59]. A retrospective study with a cohort of 219 COVID-19 patients (52 cases had critical lung parenchyma lesions, 167 had severe lung parenchyma lesions) by Leyendecker et al. showed 51 of 219 patients (23%) were diagnosed as acute adrenal infarction based on CT scan. Among these 51 patients, 45 patients (88%) presented bilateral adrenal infarction and 4 cases (8%) had acute biological adrenal gland insufficiency. Besides, the authors also indicated that the incidence of acute adrenal infraction was frequent in severe COVID-19 patients, and it was related to the higher rate of



(D) 11 February, 2003 (E) 13 February, 2003 (F) 16 February, 2003

Figure 2: The changes on chest X-ray after receiving methylprednisolone. D) The pulmonary lesions in bilateral lungs had progressed to a peak with enlarged area and increased density. E) The right lung showed diffuse patchy infiltrating shade and the left lung showed ground glass opacity with decreased density compared to the image D. F) The bilateral pulmonary lesions showed obvious absorption. The majority of left lung still showed ground glass opacity but its density continued to decrease.



(G) 19 February, 2003 (H) 23 February, 2003

Figure 3: The recovery of pulmonary lesions. G) The majority of bilateral pulmonary lesions disappeared. H) The lungs returned to normal on chest X-ray.

ICU stay and longer clinical course [60]. Another complete autopsy was performed among 28 decedents with COVID-19 in Brazil by Santana et al. and the researchers indicated that 12 of 28 cases (42.9%) presented adrenal glands. Among these cases, 7 cases showed adrenal necrosis; 4 cases showed cortical lipid degeneration; two cases had cortical hemorrhage and one had unspecific focal adrenalitis [61]. Therefore, adrenal infarct and adrenocortical insufficiency can be common lesions and complications in critically ill COVID-19 patients.

Glucocorticoid, also known as adrenocortical hormone, is secreted by the zona fasciculata of human adrenal glands. Glucocorticoids not only play a significant role in regulating metabolism of nutrition and energy, but also have powerful activity of anti-inflammation and immunosuppression [62]. Glucocorticoids modulate the metabolism level, immune system and inflammatory processes and the adrenocortical deficiency will result in decreased metabolic energy, altered immune response to infection and increased production of inflammatory cytokines [63]. Adrenal insufficiency can be divided into two kinds of diseases based on its etiology, including primary adrenal insufficiency and secondary adrenal insufficiency. Primary adrenal insufficiency means the failure of cortisol production of adrenal cortex owing to infection, trauma, cancer or autoimmune disorder, while secondary and tertiary adrenal insufficiency are attributed to the decreased secretion of Adrenocorticotropic Hormone (ACTH) in pituitary or Corticotropin-Releasing Hormone (CRH) in hypothalamus [64].

Glucocorticoids have both stimulating and inhibitory effects on immune response in different time. In the early phases of infection, glucocorticoids with physiological level can innate the human immune system. However, glucocorticoids with high level predominantly play a part in anti-inflammation and immunosuppression in the late phase of infection [65]. Therefore, the adrenal insufficiency and the suppression of Hypothalamo-Pituitary-Adrenal (HPA) axis caused by severe COVID-19 increase the risk of aggravated infection and deterioration of disease [66]. Long term glucocorticoids replacement therapy, such as hydrocortisone and cortisone, is considered as the recommendatory treatment in all cases with primary adrenal insufficiency [67]. Therefore, for those severe COVID-19 patients with adrenal insufficiency, the use of glucocorticoids does not only aim to treat pulmonary lesions, but rather to supplement the lack of physiological glucocorticoids and make the human metabolism and immune system return to normal [65]. So far, there have been not appropriate biomarkers to assess the precise dosage of glucocorticoids in replacement treatment, and so dose of glucocorticoids modification is guided based on clinical symptoms and subjective feeling of patients, as well as the levels of blood glucose and electrolyte including sodium, potassium and chlorine [64]. Thus, the glucocorticoids protocol in COVID-19 patients should be adapted to the degree of pulmonary inflammatory lesions and adrenocortical insufficiency.

Conclusion

In summary, glucocorticoids are considered as a potential effective drug to treat patients with severe COVID-19 and decrease the mortality at the moment. Although the specific mechanisms of glucocorticoids in treating COVID-19 are still controversial, this article infer that glucocorticoids may treat the potential AFOP in severe COVID-19 patients and it can be used as replacement therapy for adrenal insufficiency caused by the infection of SARS-CoV-2 based on the above literatures. More studies and research are warranted to explore the real mechanisms of glucocorticoids for treating patients with severe COVID-19 and uncover the best timing and treatment regimens of glucocorticoids.

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