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Role of Steroids and Other Immunomodulators in Treatment of COVID-19

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Coronavirus disease 2019(COVID- 19), the newly discovered infectious disease is caused by an infection with a novel virus belonging to the family Coronaviridae named severe acute respiratory syndrome coronavirus-2(SARS-CoV-2). SARS-CoV-2-infected cells produce substances that can induce injury to lung cells as the focus of initiation of COVID-19 during the incubation period. These substances bind to receptors on the target cells. Corticosteroids bind to specific intracellular cytoplasmic receptors in target tissues. The receptor hormone recruits co-activator or co-repressor proteins after dimerizing. In severe COVID-19 patients develop a systemic inflammatory response that leads to lung injury and multisystem organ dysfunction. Even though evidence consistently supporting the use of steroids in ARDS and pneumonia is hard to come by the potent anti-inflammatory effects of steroids are postulated to prevent the deleterious effects of the severe inflammation seen in COVID pneumonia. A monoclonal antibody cocktail consisting of Casirivimab and Imdevimab is another promising therapeutic option in patients at high risk of deterioration. Used early in the disease process they prevent hospitalization and further morbidity.

Keywords: Morbidity; Corona virus disease 2019; Corticosteroids; therapeutics.

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1. INTRODUCTION

Corona viruses are a group of highly diverse, enveloped, positive sense and single-stranded RNA viruses found in humans and other mammals [1]. Coronavirus disease 2019(COVID-19), the newly discovered infectious disease is caused by an infection with a novel virus belonging to the family Coronaviridae named severe acute respiratory syndrome coronavirus-2(SARS-CoV-2) [2]. It is homologous to the first corona virus that caused the 2002-2003 SARS-CoV pandemic [3,4,5]. COVID-19 has caused one of the largest global outbreaks in recent years and has affected millions of people and has caused thousands of deaths all over the world. Most of the people who are affected have mild to moderate respiratory illness and recover without requiring special treatment. Older people, people who are immunocompromised and those with underlying medical conditions are likely to develop severe illnesses that can lead to lung injury and multi- organ damage.

Administration of steroids seems to reduce risk of death in patients with acute respiratory distress syndrome as found in a retrospective study in China. Even though systemic corticosteroids might not be able to improve the mortality in critical patients, their use in the first few days of disease might enhance oxygen saturation [6]. Tocilizumab which is a inhibitor of IL-6 pathway has been found to have its effect on patients with moderate and severe COVID 19 in a controlled clinical trial. Treatment with this improved patient outcome and survival. When Tocilizumab and Dexamethasone were combinedly given to hospitalized patients with COVID 19 who had systemic inflammation and hypoxia, they showed an improved survival [7].

2. PATHOGENESIS OF COVID-19

SARS-CoV-2-infected cells produce substances that can induce injury to lung cells as the focus of initiation of COVID-19 during the incubation period [8]. These substances bind to receptors on the target cells. Innate immune system cells, neutrophils, macrophages, NK cells, immune proteins, immune peptides, nonspecific T cells and B cells comprise the first-line effectors to control various sized substances. There is cytokine storm in rapidly progressive severe COVID-19 and is associated with excessive immune cell activation against a large amount of substances [9,10]. In pneumonia, the target cells are respiratory endothelial cells, and the main substances are pathogenic peptides. Rapid and first-line immune responses at the first stage are elicited by the antibody-dependent cytotoxic reaction and the activation of cytotoxic T-cell, NK cell, and complement system pathway. Across the immune network, the initial immune reaction is less effective. Excess proinflammatory cytokines and proteolytic enzymes cause the imbalanced cytokine network which is related to target lung cell injury and can induce thromboembolic insults and fibrin leakage to the alveolar space. The products of injured target cells induce further inflammation of the neighboring lung tissue cells, immune cells, and immune proteins in the second stage.

Secondary bacterial invasion through broken lung barrier induces further inflammation and overwhelms the host's immune system. Inflammatory mediators are controlled, and inflammatory processes cease after the appearance of specific T lymphocytes and B lymphocytes. Some patients with pneumonia fail to induce immune cell clones against pathogenic proteins. High levels of pro-inflammatory cytokines and activation of nonspecific adaptive immune cells are responsible for further injury of neighboring cells. This results in a vicious cycle and manifests as chronic pulmonary disease. Early control of initial lung cell injury is crucial to prevent the progression of pneumonia. Younger children with infectious disease and infection-related immune-mediated diseases experience less severe clinical symptoms [11]. The immature adaptive immune system is less responsive against initial immune-mediated insults on target cells [12]. More severe outcomes in COVID-19 are seen in older patients with underlying diseases [13,14]. These patients lack the numerical capacity of the immune cells to respond to pathologic lesions. COVID-19 exacerbates underlying chronic diseases [15,16]. Acute exacerbation of immune-mediated diseases or immune-mediated cardiovascular disorders is caused by the mobilization of immune cells to new battlefields resulting in a fatal outcome of otherwise mild cases of pneumonia.

Older patients have higher C-reactive protein levels and erythrocyte sedimentation rates [17]. In older individuals, there is a deficiency in the production of immune cells to eliminate virions and the recombination of specific immune cell clones is less effective [18]. Pneumonia is a major risk factor; some show atypical and slow disease progression, which delays the diagnosis

of pneumonia. Patients with viral pneumonia have an invasion of commensals [19]. Antipathogen IgM and IgG antibodies appear 3–4 days after disease onset [20]. A plasma cell or a specific T-cell clone produces specific antibodies for only one protein or peptide. Antigens that induce pathogen-specific antibodies are fragments of virus proteins derived from infected cells or antigen-presenting cells that engulf virions. In SARS, some patients with severe pneumonia have a prolonged seroconversion period. Pneumonia can further progress to ARDS despite the appearance of antiviral antibodies in SARS CoV 2 [21]. At the initial focus, the patients may have few intact virions. The fragments from the replication processes in the infected cells induce immune reactions and are responsible for target cell injury and inflammation.

3. INFLAMMATORY MEDIATORS IN THE PATHOPHYSIOLOGY OF COVID-19

Inflammatory stimulus triggers the production of a network of mediators. These mediators activate each other thereby ensuring an effective and powerful defense. An anti-inflammatory response is mounted after the acute phase. Dysfunction of inflammatory response is associated with several disorders. Inflammation is involved in the pathogenesis of acute respiratory distress syndrome. This leads to alveolar oedema and hypoxemia. In acute respiratory distress syndrome, neutrophils are the predominant cell types in the pulmonary edema fluid. Neutrophils bind to the endothelial cells by the interactions between leukocyte integrins and intercellular adhesion molecules found on the endothelial surface. This contributes to the sequestration of pulmonary neutrophils [22]. There occurs release of toxic oxygen radicals, proteases, cytokines, and products of arachidonic acid metabolism which in turn damages the endothelial cells along with increased vascular permeability.

An accumulation of damage-associated molecular pattern molecules (DAMPs) and pathogen- associated molecular pattern molecules (PAMPs)occur when the signals regulating inflammatory homeostasis is altered and this contributes to the exacerbation of the inflammation [23,24]. Renal failure, acute liver injury, and cardiomyopathy can occur in the presence of severe cytokine storm. Hypoalbuminemia also occurs in the COVID-19 cytokine storm [25]. This is a consequence of liver injury and the endothelial-cell alteration with resultant capillary leak syndrome. Hypoalbuminemia and renal dysfunction may cause anasarca [26]. Hypoalbuminemia is a known factor in the causation of ARDS. Hypoxia is also caused by cardiomyopathy. Hypoxia activates neutrophils and macrophages that contribute to pneumonia and acute respiratory distress syndrome and stabilizes hypoxia-inducible factor 1α which in turn causes cytokine storm by the immune cells activation [27,28].

4. ANTI-INFLAMMATORY ROLE OF STEROIDS

Corticosteroids bind to specific intracellular cytoplasmic receptors in target tissues. The receptor hormone recruits co-activator or co-repressor proteins after dimerizing. The complexes translocate into the nucleus and attach to gene promoter elements and act as a transcription factor to turn genes on or off [29].

In general glucocorticoids,

1. Promotes gluconeogenesis, protein catabolism and lipolysis.
2. Provide the body with the energy it requires to combat stress.
3. Cause a decrease in eosinophils, basophils, monocytes, and lymphocytes and increase the levels of hemoglobin, erythrocytes, and platelets.
4. Reduce the inflammatory response and suppresses immunity.
5. Elevated glucocorticoids cause feedback inhibition of corticotropin production, thereby inhibiting the synthesis of glucocorticoids and thyroid-stimulating hormone.
6. High doses of glucocorticoids stimulate gastric acid and pepsin production, and chronic glucocorticoid therapy causes severe bone loss and myopathy.
7. Mineralocorticoids control the body's water volume and concentration of sodium and potassium.

5. PHARMACOKINETICS AND PHARMACODYNAMICS

Glucocorticoids that are administered orally are absorbed from the gastrointestinal tract. The absorbed glucocorticoids bind to plasma proteins (corticosteroid-binding globulin or albumin). They are metabolized by the liver microsomal oxidizing enzymes. The metabolites are conjugated to glucuronic acid or sulphate and the products are excreted by the kidney [29].

Table 1. Duration of action

Short acting	Intermediate acting	Long acting
Hydrocortisone	Prednisolone	Betamethasone
Cortisone	Methyl prednisolone	Dexamethasone

Table 2. Routes of administration

IM	IV, IM	Inhaled and nasal spray	Topical
Cortisone	Dexamethasone	Beclomethasone	Dexamethasone
Triamcinolone	Hydrocortisone	Budesonide	Hydrocortisone
	Methyl prednisolone	Ciclesonide	Triamcinolone
	Prednisolone	Flunisolide	
		Mometasone	
		Triamcinolone	

Based on extensive clinical experience, several therapeutic uses are proposed.

- Lung maturation acceleration: respiratory distress syndrome is a problem in premature infants. Fetal cortisol regulates lung maturation. Consequently, a dose of betamethasone or dexamethasone is given intramuscularly to the mother 48 hours before birth, followed by second dose 24 hours before delivery.
- Treatment of allergies: Glucocorticoids are used to treat symptoms of bronchial asthma, allergic rhinitis and drug, serum, or transfusion reactions.
- In neoplastic disease**:** in combination with cytotoxic drugs in the treatment of specific malignancies (e.g., Hodgkin's disease, acute lymphocytic leukemia)
- Diagnosis of Cushing syndrome**:** Cushing syndrome is caused by hypersecretion of steroids that results from an increased release of ACTH by the adrenal tumor or pituitary gland.
- Corticosteroids reduce the manifestations of inflammation associated with rheumatoid arthritis, connective tissue diseases and inflammatory skin conditions.
- Replacement therapy for primary adrenocortical insufficiency [27]

The bioequivalence and kinetics of synthetic steroids must be considered while choosing the type of steroids for treatment. Synthetic steroids have a marked anti-inflammatory action and poor mineralocorticoid effects. Hydrocortisone is the choice of steroid in the management of septic shock and associated relative adrenal Insufficiency (dose: 200–400 mg/day). Hydrocortisone has little anti-inflammatory action. Due to its shorter half-life, it should be administered every 8 hours. Methylprednisolone has a prolonged half-life and has good penetration into lung tissue. Hence it is administered once a day and is indicated in severe ARDS (dose:0.5–2 mg/kg/day). Dexamethasone is the most powerful synthetic steroid which is used for its marked anti-edema properties. It provides the most consistent duration of action. Dexamethasone is a safe drug. It gives a superior benefit-risk profile, particularly in patients with severe forms of pneumonia, while this benefit is less evident in patients with non-severe pneumonia.

6. ADVERSE EFFECTS

The use of potent corticosteroids requires knowledge of its side effects so that prompt treatment can be initiated when needed.

Osteoporosis is the most common adverse effect of prolonged steroid use. The classic Cushing-like syndrome is observed when excess corticosteroids are present. Increased incidence of cataract also occurs with prolonged steroid-therapy. Hyperglycemia may develop and lead to diabetes mellitus. Topical and inhaled glucocorticoids have the potential to cause hypothalamic pituitary adrenal axis suppression. Topical application of corticosteroids may cause skin atrophy, ecchymoses, purple striae, dermatoses, and cataract. In patients with HP Axis suppression, abrupt removal of corticosteroids causes acute adrenal insufficiency syndrome which can be fatal if not treated promptly. Other commonly observed effects of long-term corticosteroid therapy include, decreased growth in children, glaucoma, Hirsutism, Increased appetite, Hypertension, Peripheral edema, Hypokalemia, Peptic ulcer, Emotional disturbances, and Centripetal

distribution of body fat [29]. Other acute onset adverse effects like avascular necrosis and acute psychosis mandate prompt recognition and management.

As the use of steroids in the treatment of COVID is for a short duration, even at high doses, corticosteroids are not associated with serious side effects. Higher blood sugar levels are not permanent. Prolonged use of steroids for more than two weeks may be associated with adverse events such as glaucoma, cataract, fluid retention, hypertension, psychological effects, weight gain, or increased risk of infections and loss of bone strength. All these adverse events are not associated with short term use of steroids (except for hyperglycemia that can worsen diabetes) [29].

7. STEROIDS IN ARDS

Inflammation contributes to the pathogenesis of ARDS and so corticosteroids which are potent anti-inflammatory agents would seem to be a logical choice for treatment. In a meta-analysis conducted by J L Moran [30] on the usage of steroids in the prevention and treatment of acute respiratory distress syndrome, it was observed that giving corticosteroids after the onset of ARDS reduced mortality and was also associated with more ventilator-free days. In a study conducted by Meduri et al. [31] the use of methylprednisolone caused improvement in lung injury score by day 14 among 14 out of 16 patients who received the drug. Similarly in a study conducted by Rezk and Ibrahim use of methylprednisolone caused improvement in lung injury score by day 14 among 18 patients [32].

8. STEROIDS IN PNEUMONIA

Previous studies suggest that steroids increase viral load in patients with SARS COV-1 [33] which is also consistent with the data obtained following MERS [34]. It can also be seen that in patients with severe influenza infection, steroids are associated with high mortality [35]. IVIG and high-dose corticosteroids have a limited effect on advanced ARDS and there have been few randomized controlled trials. It has not been proven that these drugs are effective for reducing deaths in these groups of patients [36,37]. Cytokine storm is part of the pathogenesis of pneumonia and ARDS caused by SARS-CoV. The use of immunomodulators and corticosteroids in ARDS is currently not conclusive. Although numerous studies have been done, the heterogeneity of the trials in terms of timing of initiation, dose, type of steroids, duration of treatment and the patient population studied, makes it difficult to draw any meaningful conclusions. [38,39]. There have been few studies of early pre-emptive use of corticosteroids to reduce morbidity and mortality [40,41].

9. STEROIDS IN COVID-19

It is found that glucocorticoids have both stimulating and inhibitory effects on the immune response based on their timing and circulating levels [42]. Infections activate the hypothalamic–pituitary–adrenal (HPA) axis which leads to an increased glucocorticoid production from the adrenal glands which is responsible for mild immunosuppression, thus reducing autoimmunity and cytokine toxicity. This ability to reduce inflammation and fibrosis has been the main reason for the use of glucocorticoids in the prevention and treatment of lung damage.

Due to the homology with the structure of the original SARS-CoV; antibodies produced against SARS-CoV-2 have been hypothesized to cross-react with the ACTH peptide, contributing to a relative cortisol insufficiency [43]. Adrenal insufficiency is associated with a reduction in the natural killer cell function that impairs the recognition and elimination of virus infected cells [44]. This may be another reason to initiate steroids in COVID.

Despite having a strong pathophysiological rationale for use of steroids to control the severe immune response in COVID 19 there were initial hesitations in their use due to conflicting available evidence. [33]. In addition to the reasons mentioned earlier another confounding factor in the steroid trials is their use without considering the different pathophysiological phases of infection**.** In fact, on one hand, the supraphysiological dose of glucocorticoids shows detrimental effects in the early phase of infection (by increasing the plasma viral load), on the other hand one can argue steroids restrain the cytokine storm of the more harmful phase thereby suppressing the immune overreaction [45].

The steroid arm of the RECOVERY collaborative group trial looked at Dexamethasone use versus usual care in patients admitted with COVID, in a controlled, open-label trial. 2014 patients were assigned to receive dexamethasone and 4321

patients were assigned to receive usual care. 28-day mortality was reported in 482 of 2014 patients (22.9%) receiving dexamethasone and in 1110 of 4321 patients (25.7%) receiving usual care. So, it can be seen that,28-day mortality was lower in the dexamethasone group than in the usual care group. (p value <0.001). Death was lower in the dexamethasone group (23.3%) than that in the usual care group (26.2%) among patients receiving oxygen. Death was also lower in the dexamethasone group (29.3%) than that in the usual care group (41.4%) among patients receiving mechanical ventilation [46].

In a single-blind randomized control clinical trial conducted among severely hospitalized COVID-19 patients by Edalatifard M, Akhtari M, Salehi M, et al. [47]; 34patients were assigned to receive methylprednisolone and 34 patients were assigned to receive standard care. 94.1% of patients improved with methylprednisolone and 57.1% improved with standard care. The mortality rate was lower in methylprednisolone group (5.9%) than that in the standard care group (42.9%). The methylprednisolone group also had an increased survival time than that of the standard care group.

10. CURRENT RECOMMENDATIONS FOR USE OF STEROIDS IN COVID

The WHO recommends that Corticosteroids like dexamethasone, hydrocortisone or prednisone can be given orally or intravenously for the treatment of patients with severe and critical COVID-19 [48]. WHO contraindicates steroids usage in the treatment of non-severe COVID-19, unless the patient is already taking this medication for another illness.

A daily dose of steroids should be 6 mg of dexamethasone, which is equal to 160 mg of hydrocortisone (i.e., 50 mg every 8 hours or 100 mg every 12 hours), 40 mg of prednisone and 32 mg of methylprednisolone (8 mg every 6 hours) [48].

Corticosteroids should be taken once daily for 7-10 days.

11. IMMUNOMODULATORS

During immune responses to viral insults, the host immune cells communicate with each other via major histocompatibility complexes and cytokine networks. Interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha and immune proteins are involved in inflammation in COVID-19. Hence it is postulated that blocking the inflammatory pathways reduces inflammation-inducing substances thereby causing clinical improvement in patients with COVID.

Tocilizumab is a monoclonal antibody, directed against the IL-6 receptor. It is considered in patients with the moderate disease having raised IL-6 and increasing oxygen demand, unresponsive to other therapy. It reduces the risk of invasive mechanical ventilation or death in patients with severe COVID-19 pneumonia. In a study conducted to assess the efficacy of Tocilizumab in a single center cohort of COVID-19 patients requiring mechanical ventilation by Emily C Somers, [49] among 154 patients, 78 were treated with Tocilizumab. Survival probability was higher among Tocilizumab treated patients(p=0.189).
In hospitalized COVID-19 patients with severe symptoms of hypoxia and systemic inflammation, Tocilizumab improved survival rates and other clinical outcomes. These advantages of this drug were seen in the addition of respiratory support and to the benefits of systemic corticosteroids [50]. In a trial conducted by Anthony C. Gordon [51] among critically ill patients with Covid-19, who are receiving organ support in ICU, treatment with the IL-6 receptor antagonist Tocilizumab and Sarilumab improved the survival rates. The mean adjusted odds ratio for primary hospital survival was 1.66 for tocilizumab, 2.25 for sarilumab and the probability of superiority to the control group was more than 99.6% in Tocilizumab and99.5% in Sarilumab.

Baricitinib is an oral Janus kinase inhibitor. It is used for the treatment of rheumatoid arthritis (RA) and found to be useful for COVID-19 infection by a proposed anti-cytokine effect and as a host cell viral propagation inhibitor by artificial intelligence (AI) algorithms. Baricitinib treatment gave clinical and radiological recovery in patients with bilateral COVID-19 pneumonia, a rapid decline in SARS-CoV-2 viral load, inflammatory markers, and IL-6 levels [52].

In an observational and longitudinal trial in severe COVID-19 patients conducted by Bronte V [53], 20 patients were treated with Baricitinib while 56 did not receive the drug. Patients treated with Baricitinib had a faster reduction in the need for oxygen therapy. They had a rapid increase in P/F ratio (Oxygen partial pressure/ Fraction of inspired oxygen) when compared with the control group. It reduces the plasma

concentration of proinflammatory cytokines, that contribute to cytokine storm. It also increases antibody production against SARS COV2 spike proteins.

Casirivimab and Imdevimab are monoclonal antibodies which are directed against the spike protein of SARS-CoV-2 designed to block the virus attachment and entry into human cells. In a randomized, controlled, open label, platform trial to assess the efficacy of Casirivimab and Imdevimab in patients admitted to hospital with COVID-19, 9785 patients were allocated to receive usual care plus Casirivimab and Imdevimab or usual care alone. Among the 9785 patients, 3153 were seronegative, 5272 were seropositive and 1360 with unknown baseline antibody status. Among the seronegative patients, 396 allocated to the drug and 451 allocated to usual care died within 28 days (p value 0.0010). Among all randomized patients, 944 allocated to the drug and 1026 allocated to usual care died within 28 days (p value 0.17). Thus, Casirivimab and Imdevimab reduced 28day mortality among patients who were seronegative [54].

12. CONCLUSION

In severe COVID-19 patients develop a systemic inflammatory response that leads to lung injury and multisystem organ dysfunction. Even though evidence consistently supporting a use of steroids in ARDS and pneumonia is hard to come by the potent anti-inflammatory effects of steroids are postulated to prevent the deleterious effects of the severe inflammation seen in COVID pneumonia. Fears of delayed clearance of virus as seen in outbreaks of MERS and SARS resulted in an initial hesitation to use steroids in the treatment of COVID pneumonia. However recent evidence has proven steroids to be lifesaving in severe COVID disease. However, the tendency to use steroids in higher doses and for a prolonged period in these patients is one fraught with danger and needs to be curbed. Similarly, after the initial conflicting evidence more recent studies have supported the use of Immunomodulators like Tocilizumab in curbing cytokine storm in patients who continue to worsen despite optimum therapy. A monoclonal antibody cocktail consisting of Casirivimab and Imdevimab is another promising therapeutic option in patients at high risk of deterioration. Used early in the disease process they prevent hospitalization and further morbidity.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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