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Mini-review

The effectiveness of dexamethasone as a combination therapy for COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) was reported as a global pandemic in March 2020 after invading many countries and leaving behind tens of thousands of infected patients in a brief time span. Approval of a few vaccines has been obtained and their efficacy of varying degrees established. Still, there is no effective pharmaceutical agent for the treatment of COVID-19 though several drugs are undergoing clinical trials. Recent studies have shown that dexamethasone, a corticosteroid, can reduce the rate of COVID-19-related mortality in the intensive care unit by 35 % for patients who are on mechanical ventilation. Although variable efficacy of other combination therapies has been reported for treating COVID-19 associated with acute respiratory distress syndrome (ARDS), dexamethasone is an extensively used drug in many treatment regimens against COVID-19. The current review aims to explore the role of dexamethasone as an efficient combination treatment for COVID-19.

Keywords: dexamethasone, glucocorticosteroids, acute respiratory distress syndrome, Coronavirus disease 2019, combination therapy, SARS-CoV-2, immunosuppressive

INTRODUCTION

In early December 2019, a highly infectious pneumonia-like disease surfaced in Wuhan, China, as a result of a novel coronavirus that caused severe comorbidities. This epidemic named coronavirus disease 2019 (COVID-19), spread in a short duration of time all over the world and had a serious impact on public health as well as on the global economy. A substantial number of patients suffered from a respiratory illness that required hospitalization due to severe acute respiratory syndrome (SARS). As of December 2021, more than 290 million COVID-19 cases have been reported globally with 5.4 million deaths. Most of the cases either resulted in mild diseases or remained asymptomatic. However, in patients with respiratory ailments, the disease progressed to a critical illness that required prolonged ventilation (1). In patients with comorbidities, COVID-19 was the most severe with a fatal outcome.

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At present, there is a gradual fall in the number of COVID-19 cases due to immediate clinical intervention and massive vaccination programs. Nonetheless, the virus continues to spread across the globe, emerging as a mutated and more resistant variant (2).

In COVID-19 patients, corticosteroids and other anti-inflammatory drugs have been used to mitigate the lung damage caused by the cytokine storm (3). Owing to their rapid anti-inflammatory and immunosuppressive effects, corticosteroids have been extensively employed in the treatment of the former coronavirus diseases such as the Middle East respiratory syndrome (MERS), severe acute respiratory syndrome (SARS) and other such hyper-inflammatory conditions. In contrast, clinical studies related to the use of corticosteroids for the treatment of patients with COVID-19 (also called SARS-CoV-2), are limited (4). There is an incongruity in these studies with regards to the dose, duration and type of corticosteroid therapy and the susceptibility of the patients to the drug.

All glucocorticosteroids attenuate the immune response by reversing proinflammatory cytokines and chemokines associated with viral infections (5). A multitude of drugs have shown effectiveness against SARS-CoV-2; however, dexamethasone was the first drug that reduced COVID-19-associated morbidity and mortality (6). Dexamethasone has been used in the treatment of several disease conditions such as allergy, asthma, chronic obstructive pulmonary disease, rheumatic disease, skin disorders, cerebral edema and in parallel with antibiotics in tuberculosis. This review highlights the effectiveness of dexamethasone as adjunctive therapy for COVID-19.

PATHOPHYSIOLOGICAL FEATURES OF COVID-19

It is well-known that most of the severe cases and mortalities associated with SARS-CoV-2 are the result of overreaction of the immune system and subsequent hyperinflammation. Most of the COVID-19 patients do not show serious clinical manifestations in the initial phase of the disease (7, 8). The symptoms aggravate at the late stage, whereby the conditions deteriorate suddenly. Cytokine release is considered to be the foremost concern in COVID-19 where acute respiratory distress syndrome (ARDS) occurs rapidly and progresses to multiple-organ failure within a short time.

There is a lack of information on the pathophysiology of COVID-19. The virus enters through the upper respiratory tract and binds to the nasal epithelial cells. Angiotensin-converting enzyme-2 (ACE-2) receptors are expressed predominantly in the lung tissue which is considered as the main host for viral infection (9). After binding to ACE-2 receptors by the S protein subunit, the S protein is cleaved by the transmembrane serine protease 2 (TMPRSS2), facilitating the cellular entry and consequent viral replication and propagation, which is specifically described as an invasion of type-II pulmonary alveolar epithelial cells and capillary endothelium. In the early phase, viral replication results in the generation of a limited immune response (Fig. 1). Whereas, in the late phase, infected cells stimulate an immune response and subsequent release of cytokines such as tumour necrosis factor-alpha (TNF-α), granulocyte monocyte colony-stimulating factor (GM-CSF), interleukin (IL)-1, IL-6, IL-1β, IL-8, IL-12 and interferon-gamma (IFN)-γ. These triggered cytokines produce a robust immune response which leads to ARDS (10). Acute COVID-19 in the late-stage damages the lungs and various organs leading to multiple organ exhaustion (11). The most adverse outcomes of COVID-19 include excessive inflammation and pulmonary injury secondary to ARDS ensuing diffused alveolar damage.

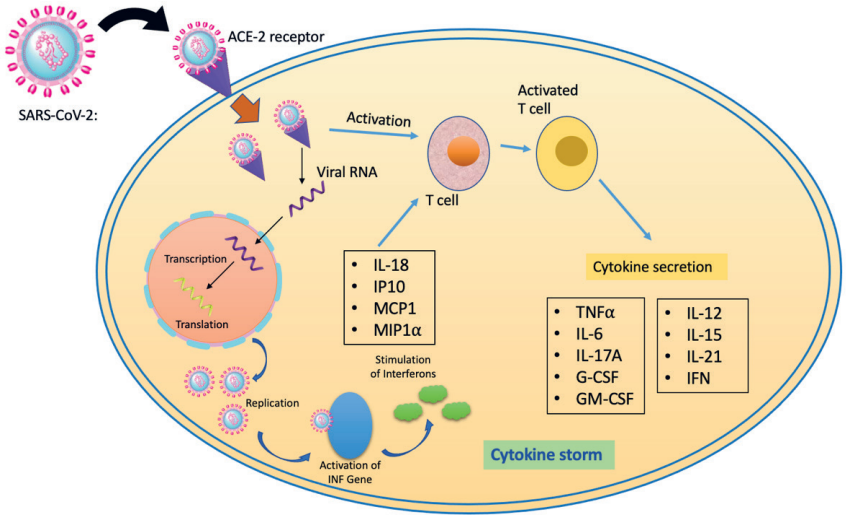

Fig. 1. Schematic representation of SARS-CoV-2 pathogenesis in epithelial cell and cytokine storm (reproduced from ref. 67). The SARS-CoV-2 virus enters through the naso-oral route and attacks alveolar cells expressing the ACE-2 receptor. The virus avoids the innate immune cells, such as monocytes, macrophages and neutrophils, as a result of unrestrained virus replication leading to increased pro-inflammatory cytokines. This induces activation of helper T-cells and aggravates the inflammatory responses, resulting in a cytokine storm.

This cytokine storm attracts neutrophils, $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells which then get accumulated in the lung tissue and begin to fight off the virus, resulting in subsequent inflammation and lung injury. In addition, the severe symptoms in COVID-19 patients are essentially due to this cytokine storm wherein the immune system

Table I. Symptoms and severity of COVID-19 disease

Incidence	Symptoms
Common	Pulmonary embolism
	Acute respiratory distress syndrome (ARDS)
	Pneumonia
	Blood infections
	Acute liver injury
	Kidney injury
	Intravascular coagulation
Unusual	Pancreatitis
	Neurological complications
	Autoimmune haemolytic anaemia
	Aspergillosis
	Multisystem inflammatory syndrome

gets hyperactivated (11, 12). This leads to the release of IL-6 and TNF-α into the circulation, inducing local and systemic inflammation and coagulation abnormalities, culminating in organ failure and death. These complications are summarized in Table I.

Clinical intervention of COVID-19

The current clinical intervention of the disease involves water/electrolyte balance, nutritional support, oxygen supplementation, supportive care and antiviral therapy with interferon-α, hydroxychloroquine, remdesivir, lopinavir, ritonavir, ribavirin, or arbidol. However, these drugs mostly relieve the symptoms in the early stages and there is no specific therapy for COVID-19 so far (13, 14). Table II depicts potential interventions for COVID-19 related ARDS. IL-6 inhibitors have been recommended by the UK COVID-19 guidelines as well as the Infectious Diseases Society of America for patients with severe COVID-19 (15).

COVID-19 patients who recover and show the following signs of improvement could be discharged from the hospital: (*i*) significant improvement of the respiratory symptoms, (*ii*) normal body temperature for three consecutive days, (*iii*) significant improvement of the acute exudative lesions upon pulmonary imaging, (*iv*) negative reports of at least two nucleic acid tests for SARS-CoV-2 (16).

Glucocorticoids for COVID-19 therapy

Immune system over-reaction and subsequent hyperinflammation have mostly been recorded in a significant number of COVID-19 cases. Glucocorticoids have been extensively used to control acute and chronic inflammatory and autoimmune diseases. To date, there

Table II. Clinical intervention of COVID-19

Drug	Study title	Location	Status	Clinical trial code[a]
Dexamethasone	Efficacy study of dexamethasone to treat the acute respiratory distress syndrome	Spain	Completed	NCT01731795
Dexamethasone or methylprednisolone	Dexamethasone *vs*. methylprednisolone for the treatment of patients with ARDS caused by COVID-19	Bangladesh	Recruiting	NCT04499313
Remdesivir and baricitinib	Efficacy of ramdicivir and baricitinib for the treatment of severe COVID 19 patients	Bangladesh	Recruiting	NCT04693026
Sevoflurane	Sevoflurane in COVID-19 ARDS (SevCov)	Switzerland	Completed	NCT04355962
Cyclosporine	Safety and effectiveness of cyclosporine in the management of COVID19 ARDS patients in Alexandria University Hospital	Egypt	Recruiting	NCT04979884
Pirfenidone	Treatment with pirfenidone for COVID-19 related severe ARDS	Israel	Recruiting	NCT04653831

[a] www.clinicaltrials.gov

is a debate regarding the effectiveness of glucocorticoids for the treatment of critically ill COVID-19 patients associated with ARDS. Although the intervention with glucocorticoids has been reported to cause severe complications, in China, COVID-19 patients have been widely treated with glucocorticoids, especially in cases with ARDS. Glucocorticoids have been found to mitigate SARS-CoV-2 infection by lowering the IL-6 levels. Amongst the glucocorticoids family, dexamethasone has been reported as the drug of the first choice for the treatment of respiratory diseases such as asthma and tuberculosis (17–19).

Dexamethasone as first-choice therapy for COVID-19

Dexamethasone is the only drug that has shown an improved survival rate in COVID-19 patients. The drug is widely available and extensively prescribed (20). Preliminary reports have indicated that dexamethasone decreased the death rate in patients with COVID-19 who were only on oxygen support. Early intervention with small doses of dexamethasone in patients with hyperinflammatory responses associated with rising C-reactive protein (CRP) levels has also been reported. The study postulated the effect of a low dose of dexamethasone

Table III. Major clinical trials efficacy of dexamethasone treatment for patients with COVID-19

Clinical trial code[a]	Title	Status	Phase	Population	Country
NCT04513184	Randomized clinical trial of intranasal dexamethasone as an adjuvant in patients with COVID-19	Recruiting	Phase 2	60 individuals	Mexico
NCT05062681	RCT on the efficacy of dexamethasone *versus* methyl prednisolone in Covid-19 infected patients with high oxygen flow	Recruiting	Phase 4	60 individuals	Egypt
NCT04726098	Low or high dose of dexamethasone in patients with respiratory failure by COVID-19	Completed	Phase4	198 participants	Spain
NCT04663555	Effect of two different doses of dexamethasone in patients with ARDS and COVID-19	Recruiting	Phase 4	300 participants	Czech Republic
NCT04707534	Dexamethasone for COVID-19	Recruiting	Phase 4	300 participants	United States of America
NCT04909918	Impact of steroids on inflammatory response in Covid-19	Completed	Phase 3	60 participants	Egypt
NCT04445506	Short term corticosteroids in SARS-CoV-2 patients	Completed	–	50 individuals (18 years and older)	United States of America

[a] www.clinicaltrials.gov

as an adjunct therapy for COVID-19. Many guidelines recommend using the lowest possible dose of dexamethasone, and avoiding sudden discontinuation in moderate to severe COVID-19 (21).

A clinical trial performed in the United Kingdom on patients hospitalized with COVID-19 who received dexamethasone revealed a drop in mortality rate compared with those who had received standard treatment (21). Contrary to this, few researchers did not support corticosteroid therapy of critically ill COVID-19 pneumonia patients admitted in the intensive care unit (ICU) (22). Table III shows the major clinical trials in which the therapeutic potential of dexamethasone in COVID-19 patients has been evaluated.

Pharmacology of dexamethasone

Dexamethasone is a synthetic corticosteroid that has both immunoregulatory and anti-inflammatory properties. It decreases vasodilation and permeability of capillaries, as well as reduces leukocyte migration to the sites of inflammation (23). Dexamethasone is a small lipophilic anti-inflammatory glucocorticoid receptor (GCR) agonist with various clinical indications (Fig. 2). As an FDA approved drug for treating tuberculosis, dexamethasone has also demonstrated effectiveness in treating COVID-19 patients (24).

Dexamethasone has diverse mechanisms of action which depend on the dosage (25, 26). At a low dose, dexamethasone binds to its receptor (GCR) on the cell membrane and post-nuclear translocation, it binds reversibly to several specific DNA sites. This suppresses the gene transcription of a large variety of pro-inflammatory cytokines, chemokines, and adhesion molecules (Fig. 3). On the other hand, at a high dose, the effect of corticosteroid therapy may be counterproductive. Dexamethasone as a broad-spectrum immunosuppressant promotes antibody production from B cells, reduces the T cell-protective function, and suppresses macrophage-mediated clearance of apoptotic cells. This results in an elevated plasma viral load and heightened susceptibility to secondary infections. Moreover, treatment with a high dose of dexamethasone hinders the cycling of Ca^{2+} and Na^{+} across the cell membrane leading to a rapid decline in inflammation.

Dexamethasone indications and dosing

During the hyperinflammatory phase involved in patients with pneumonia due to COVID-19, dexamethasone has been found to be the only life-saving drug that showed efficacy in a short course of treatment (14).

The dose of dexamethasone depends upon the patient's response. As far as possible, low dosage should be used in order to minimize the adverse effects associated with the

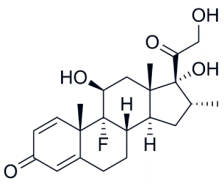

Fig. 2. The chemical structure of dexamethasone.

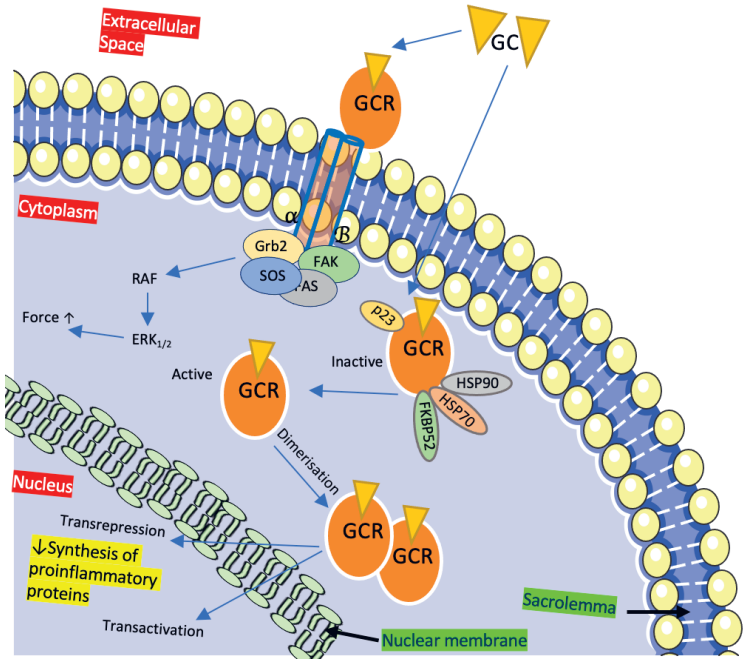

Fig. 3. A schematic diagram of the glucocorticoids' (GC) mechanism of action (reproduced from ref. 68). The glucocorticoids manifest their effects by binding to the intracellular glucocorticoid receptors (GCR). A change in gene transcription occurs after GCR dimerization and translocation from the cytoplasm into the nucleus. GCR then binds to glucocorticoid response elements (GRE) resulting in changes in the synthesis of mRNA and subsequently in protein synthesis.

chronic treatment. Intravenous or oral administration of 6 mg per day of dexamethasone for 10 days has been reported to reduce the death rate by 35 % in patients who were on mechanical ventilation in the ICU (21, 23). In more severe conditions, a dose higher than 10 mg per day may be considered.

Dexamethasone-dependent adverse effects

The usual side-effects of dexamethasone include headache, increase in appetite and mood swings. Occasionally, it results in agitation and blurred vision with dizziness. It has been known that patients who receive a large dose of corticosteroids have a 20 % chance to acquire neuropsychiatric disorders including mania, psychosis and depression that require treatment intervention. Due to the powerful immunosuppressive effect, all corticosteroids are associated with several side effects, both psychological and physiological which are potentially harmful to COVID-19 patients (27, 28).

Treatment with dexamethasone can cause organ dysfunction and result in many side effects. Many researchers do not suggest chronic use of dexamethasone especially for severe COVID-19 based on the treatment history of SARS patients (29, 30).

Table IV. Dexamethasone-dependent adverse effects

System	Complications	Ref.
Cardiovascular	Hypertension, accelerated atherosclerosis	33, 34
Dermatologic	Acne, alopecia, hirsutism, striated skin atrophy, purpura	35
Endocrine	Obesity, diabetes mellitus	36, 37
Gastrointestinal	Peptic ulcer, pancreatitis, fatty liver, bowel perforation	32, 38–40
Infectious	Oral candidiasis	41
Musculoskeletal	Myopathy, osteoporosis, vascular necrosis	42, 43
Ophthalmologic	Cataract, glaucoma	44, 45
Renal	Renal calcification, nephrocalcinosis	46, 47
Central nervous system	Psychosis, mania, depression	48, 49

Although dexamethasone is recommended for COVID-19 treatment, it is critical to observe the function of essential organs for damage caused by the chronic use. Table IV outlines the major adverse effects that are accompanied with dexamethasone treatment, especially when it is used as a combination therapy (31, 32). Studies have shown that dexamethasone is not effective in the treatment of COVID-19 cases with hyperactive inflammatory stage because it takes a long time to exert any notable therapeutic effect.

Combination therapy for COVID-19

COVID-19 is a biphasic illness necessitating distinct treatments in each phase (50). The effect of a single therapeutic agent is limited compared to promising drug combinations for COVID-19. Clinicians have been focusing on using a combination of medicines to treat COVID-19 in view of the immune system responding differently to different drugs. Some of the drugs used in combination therapy include hydroxychloroquine, chloroquine, remdesivir, lopinavir and corticosteroids. These drugs may help to hasten the recovery but at times, do not have any positive outcome. Due to their rapid anti-inflammatory and immunosuppressive effects, corticosteroids have been prescribed in severe coronavirus diseases such as MERS, SARS and SARS-CoV-2 to curb the immune-mediated tissue damage in the lungs.

Izumo *et al*. (51) compared the effectiveness of the combination therapy of severe COVID-19 with remdesivir, dexamethasone, and tocilizumab (RDT) with respect to the mortality rate and adverse side effects. A plethora of drug combinations has been used to mitigate the severity of COVID-19 (52, 53).

Concurrent therapy with a glucocorticoid and nitric oxide is another promising combinatorial approach for treating COVID-19. This combination can potentially prevent excessive mucus production by goblet cells and subsequent airway occlusion (54). It is known that under certain pathological conditions, mucus hypersecretion occurs as a consequence of alveolar damage in the lungs. Combination therapy with glucocorticoids and nitric oxide alleviates airway occlusion in COVID-19 patients.

Dexamethasone as an adjunct therapy for COVID-19

Dexamethasone is not preferred as monotherapy for COVID-19 patients who are on mechanical ventilation because of high dose requirements for a prolonged time that is associated with many adverse reactions (32, 55). Furthermore, prolonged treatment with dexamethasone can lead to the development of resistance against corticosteroids. Moreover, dexamethasone has been used ordinarily as adjuvant therapy for severe influenza cases as well as in the treatment of ARDS (56).

Recent research indicates that the concentration of dexamethasone in the blood may dictate its stimulatory or inhibitory effect on the immune system (57). In order to maximise the therapeutic effect of dexamethasone in COVID-19 patients, while mitigating its complications arising from higher drug dosage or chronic use, a chemocentric informatics approach has been reported to identify the potential drug combinations that could effectively combat COVID-19 (58).

A combination therapy that augments the anti-inflammatory and immunosuppressant activity of dexamethasone is required. It has been reported that combination therapy consisting of dexamethasone with a long-acting beta-2 adrenergic agonist (LABA) has shown promise in alleviating COVID-19-related ARDS. Such a combination may yield a suppression of inflammatory and immune responses and immediate bronchodilatory and vasodilatory effects (56, 59, 60). Combining dexamethasone with LABA, such as formoterol and salmeterol, improves anti-inflammatory as well as fibronectin-mediated anticoagulant effects and relieves respiratory distress to rescue COVID-19 patients (50). The benefit of this combinatorial therapy is the accelerated action of LABAs in deactivating proinflammatory cytokines, in comparison to dexamethasone. Another benefit of this adjunct therapy is the reduced fibronectin production due to potential antifibrotic action that stems from suppressed transforming growth factor beta-1 signaling in airway fibroblasts and myofibroblasts (61, 62). Patients on a combinatorial therapy of LABA and inhaled dexamethasone culminated in a rapid amelioration of symptoms leading to a better lung function in comparison with those receiving either drug alone (63).

Observational data suggest that tocilizumab with dexamethasone is an effective intervention to reduce the mortality rate from severe COVID-19 due to ARDS (64). The additive effect of both remdesivir and dexamethasone could be possible if the antiviral agent is administered prior to corticosteroids to clear out the virus from the host. Then, the corticosteroids might attenuate the severity of acute lung injury by reducing the inflammatory response. Immediate clinical intervention with IL-6 inhibitors and dexamethasone prior to the exacerbation of COVID-19 has been found to be associated with reduced mortality and could improve the outcome of the treatment.

The combination therapy for COVID-19 disease was found to be cost-effective for both ventilated and non-ventilated ICU patients by decreasing the length of hospitalization. This review strongly supports the necessity of dexamethasone as a first-line treatment for ICU patients with COVID-19 in parallel with antiviral agents for shortening the hospitalization period (65, 66).

CONCLUSIONS

COVID-19 is a unique infectious disease which entails a combination therapy of more than two drugs rather than relying on a single type of treatment. A substantial percentage

of COVID-19-infected patients require oxygenation and ventilation. To reduce COVID-19-related morality rate and recovery time, potential combination therapy is now recommended especially for severely or critically ill patients. There are many common adjuvant therapies that have delineated beneficial effects in ARDS through modulating cytokine responses and regulating the functions of immune and non-immune cells. Dexamethasone is considered a cost-effective early intervention for COVID-19. However, treatment with higher doses for prolonged periods could lead to severe complications and subsequent treatment failure.

Acronyms, abbreviations, symbols. – ACE-2 – angiotensin-converting enzyme-2, ARDS – acute respiratory distress syndrome, COVID-19 – Coronavirus disease 2019, CRP – C-reactive protein, GC – glucocorticoid, GCR – glucocorticoid receptor, GM-CSF – granulocyte monocyte colony-stimulating factor, GRE – glucocorticoid response elements, ICU – intensive care unit, IFN-γ – interferon-gamma, IL – interleukin, MERS – Middle East respiratory syndrome, SARS – severe acute respiratory syndrome, TMPRSS2 – transmembrane serine protease 2

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