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How Does Dexamethasone Work Against the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)?

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Abstract

The continuing COVID-19 pandemic instigated by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) led the scientists discover an array of candidate drugs and set up possible vaccine platforms under trial. However, till date no vaccines have been established to abate COVID-19 pandemic while a few drugs as the anti-virals or the immunomodulators have been proposed on the basis of patient trial success. One of them is remdesivir which is actually a broad spectrum anti-viral drug. Recently, the corticosteroid dexamethasone has evolved with a stunning property to cure the COVID-19 patients who have developed the Acute Respiratory Syndrome (ARDS), requiring ventilation. Several recent case studies have shown the efficacy of dexamethasone to treat the severe patients who were at the risk of death. Present review focused on the mechanism of action of dexamethasone with its specific immunological functions in course of curing the SARS-CoV-2 infection within a patient. A model regarding the mechanisms of dexamethasone action has been proposed as well.

Keywords

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); Drugs; Vaccines; Dexamethasone; Model of Mode of Action

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Introduction

Re-emerging viruses are continuously posing health threat towards the global public health [1-3]. Present COVID-19 pandemic triggered by the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) has brought the global public health at its higher risk already accounting for 1,039,406 deaths out of 35,347,404 infected cases worldwide [4]. Although several candidate DNA and RNA vaccines, the recombinant vaccines and some others are currently under trial (maximum within Phase I-II and a few entering the Phase III trial), still no satisfactory vaccine could be endorsed for the Phase IV trial let alone getting the biological license or for the commercial production [5-7]. Besides, the computer simulation studies, the cell culture experiments, the clinical trials have projected some potential candidate drugs like ribavirin, remdesivir, favipiravir, chloroquine and hydroxychloroquine; favipiravir and opinavir/ritonavir of which remdesivir has so far been noticed to be the most effective in mitigating the viral infection with the mode of action to suppress the RNA polymerase [8]. Indeed, lots of research reports showed that upon the entry of SARS-CoV-2 into the host cell through the viral Spike (S) protein-ACE 2 receptor interaction within the Receptor Binding Domain (RBD), an event of cytokine storm (i.e., the abnormal elevation of the cytokines and chemokines) takes place; and ironically the Antibody (mainly Immunoglobulin M or IgM) Dependent Entry (ADE) of the virus may also simultaneously occurs [5-7]. Thus the response of the innate immunity and the adaptive immunity apparently goes against the infected individual leading to the onset of the Acute Respiratory Distress Syndrome (ARDS) accompanied with the major organ malfunction [8-10].

A contemporary investigation showed that a new drug to evolve to combat the COVID-19 and that is the dexamethasone which is a synthetic adrenal corticosteroid possessing the anti-inflammatory properties against the mass accumulation of the innate immune cells (macrophages, dendritic cells, neutrophils, etc.), the pro-inflammatory cytokines and the effectors ranging an array of interleukins and other factors resulting in the inflammation of lungs [8]. The effectiveness of dexamethasone has been well observed through the recovery of severely affected patients who needed the external oxygen supply or ventilation [11,12]. Present review, employing a proposed model, focused on the probable mode of action of dexamethasone and on the possible target sites to remediate SARS-CoV-2.

Dexamethasone as a Candidate for the Treatment of Severe Cases of COVID-19: Possible Mode of Action

What Happens after the Entry of SARS-CoV-2 into the Host?

The SARS-CoV-2 starts its journey along the nose, mouth, or eyes and travels down to the alveoli in the lungs. The Spike (S) protein covering the coronavirus binds with ACE2 receptors

that are primarily on type II alveolar cells (Fig. 1). After infecting the cells, the virus goes through active replication and then the release of more new virus cause the host cell to release Damage Associated Molecular Patterns (DAMPs) which are recognized by the neighbouring epithelial cells, endothelial cells and alveolar macrophages, triggering the elevation of the pro-inflammatory cytokines and chemokines including IL-6, IP-10, macrophage inflammatory protein 1 α (MIP1 α), MIP1 β , MCP1 [6]. This triggers a cascade of reaction that attract monocytes, macrophages and T-cells to the site of infection and enhancing further inflammation (with the addition of IFN γ produced by T cells). Thus, during SARS-CoV-2 infection, the immune system becomes defective leading to further accumulation of immune cells in the lungs, causing overproduction of pro-inflammatory cytokines, which eventually damages the lung infrastructure. Due to high vascular permeability, fluid accumulates inside the alveolus where neutrophils are recruited to the site of infection and release reactive oxygen species to destroy infected cells [13]. Type I and II cells are destroyed, leading to the collapse of alveolus and causing ARDS [8-10].

How does dexamethasone prevent the COVID-19 severity?

The corticosteroid dexamethasone, a broad-spectrum immunosuppressor is already known to reduce inflammation and the inflammatory disorders to limit the inflammatory cytokines and chemokines to block excessive accumulation macrophages and dendritic cells [1,2,12,14]. Simply still there is no medicine including remdesivir or other so called potential candidate antivirals which can actually save lives of the severely infected COVID-19 patients and in such defenceless state of the COVID-19 pandemic, dexamethasone has come up with its ground breaking potential to cure the patients (at least by a success rate of 35%) who underwent near to death [11,12,15]. Another interesting point is that dexamethasone can indirectly prevent the ADE based entry of the SARS-CoV-2 particles (Fig. 1) thereby diminishing the viral shedding along with its potential to hinder the mast cell activity of the innate immune system which in turn may aid to bring back the equilibrium within the infection rate and the host immune response. As stated earlier, upon entry of the virus particles, the hyper-inflammation is induced by the disproportionate accumulation of the innate immune cells including the eosinophils, macrophages, dendritic cells, mast cells and others (Fig. 1). Inflammatory cytokines and chemokines, lipid mediators and growth factors leading to lung inflammation as well as severe asthma and ARDS [16]. Dexamethasone may decrease such undue gathering of the inflammatory cells thereby reducing the cytokine storm (Fig. 1) which in turn decrease the lung inflammation [16]. Besides, as mentioned above, dexamethasone plays an important role in blocking the viral entry into the host cell. Therefore, this corticosteroid drug mainly functions both as the inhibitor of the viral entry; and as immunomodulatory to keep the concentration of cytokines and chemokines in harmony even after the viral entry into the cell (Fig. 1). The third protective mechanism underlies under its capacity to inhibit the inflammatory mast cells into the airway passage [17].

Figure 1: Proposed model for the mode of action of dexamethasone. The corticosteroid drug mainly inhibits the cytokine storm and may block the Antibody Dependent Entry (ADE) of SARS-CoV-2 into the host. Details are given in the text.

Conclusion

As understood from the current review, the viral entry and the immunomodulation are the two principal suggestive mode of action for dexamethasone. The proposed model simply showed the drug targets and the consequences on the host immune response. Such knowledge may be incremental to some extent for the effective drug designing to combat the COVID-19 pandemic.

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