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Modulating inflammation in COVID-19 viral disease: The emerging role for dexamethasone

Osagie A. Emokpae[1,2*], Promise O. Osemwenkhae[1], Osakpamwan F. Odigie[1], Osayuki N. Omoregie[1], Erhagbe Benedicta[1], Ben-Azu Benneth[3]

[1]Pharmacy Department, University of Benin Teaching Hospital, Ugbowo, Benin City, Edo State, Nigeria
[2]Department of Pharmacology and Toxicology, Professor Dora Akunyili College of Pharmacy, Igbinedion University Okada, Edo State, Nigeria
[3]Department of Pharmacology and Therapeutics, Delta State University, Abraka, Delta State, Nigeria

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* *Corresponding Author:*
emokpae78@gmail.com
Tel: +2348162419471
https://orcid.org/0000-0001-5178-1212

ABSTRACT

Background: The global scientific community continues to saddle one of the responsibilities of constraining the menace caused by Coronavirus Disease 2019 (COVID-19); a relatively novel corona virus infection that has metamorphosed to becoming a pandemic. Epidemiological evidence shows that it is responsible for over 1.7 million death worldwide. Besides, the pandemic has negatively impacted vital sectors of national economy and government such as employment of labor, transportation, national budgets and financial business progression. Conversely, the times have driven scientists, medical experts and health professionals to thinking up newer and safer therapeutic strategies in order to better manage and combat the virus. While several therapeutic approaches have been unveiled by researchers, this article lays emphasis on modulating inflammation in COVID-19 viral disease with respect to an emerging role for dexamethasone. Crosstalk between pathogenesis of Severe Acute Respiratory Syndrome-related Coronavirus-2 (SARSr-CoV-2) and inflammation remains invaluable to unraveling other alternative drug targets that may pose as probable paths towards mitigating the effects of the virus in humans.

Methods: The roles of angiotensin converting enzyme-2 protein in mediating the transfer of SARSr-CoV-2 into epithelial cells of the mucosal membranes of the conjunctiva and oral cavity was evaluated. Also, viral antigen presentation in the cells was evaluated as a trigger to an immunological reaction that results in a cytokine surge in the blood, downplay of lymphocytic cells and upregulation of other chemical mediators of inflammation. This eventually actuates the hemostatic system to trigger pro coagulating factors and thrombo-inflammatory responses, which may ultimately lead to fibrosis and other respiratory disorders.

Conclusion: The ameliorative effect of dexamethasone, a commonly used glucocorticoid for treating inflammatory disorders remains striking and significant in SARSr-CoV-2 management. Contrary to data gotten from previous studies of glucocorticoids effect on earlier existing corona viruses, recent findings have reported that dexamethasone possess some beneficial effects in attenuating pulmonary derangements caused by SARSr-CoV-2. Moreover, this brings to limelight and further buttresses the relationship between inflammation and COVID-19 pathology. Hence, the need to discover newer or repurpose preexisting drug molecules that may target inflammatory signaling cascades in COVID-19 viral disease is imperative.

1. Introduction

Corona viruses are enveloped viruses, belonging to the sub family *Coronaviridae*, and constituting part of the larger family *Orthocoronavirinae* [1]. They cause a range of diseases in mammals and birds, including, but not limited to respiratory infections, diarrhea, and hepatitis [2]. Examples of corona viruses include: Middle East Respiratory Syndrome-related Coronavirus (MERSr-CoV), Severe Acute Respiratory Syndrome-related Coronavirus (SARSr-CoV), Beta coronavirus, Avian Coronavirus, Torovirus, Gammacoronavirus, Cegacovirus, and Hedgehog Coronavirus I[1]. Most early infectees of the Corona Virus Disease (Covid) -19 were workers at the Huanan Seafood

market in Wuhan, China, where the virus is reported to have emanated [3]. However, other researchers have suggested that visitors from across the globe may have introduced the virus into the market, which then increased spread of the disease[3]. Most scientists also think the virus originated in bats, but how it got transmitted to people remains fully unknown [4]. COVID-19 pandemic left economies and businesses counting the costs, with more countries plunging into recession, while decreasing the number of commercial flights and inter-state travels, thus, impacting negatively on the global tourism and trade industry [5].

Government has however, come up with new protective measures to curb the spread of the virus such as encouraging the use of face masks, social distancing, and regular washing of hands [6]. More-so, there has been several positive contributions from healthcare regulating agencies, research institutions and non-governmental organizations to quicken the process of drug and vaccine discovery to better treat or prevent the spread of the infection[6]. Some vaccines have since been developed, with different countries getting relief supplies, and many are still wondering what a full recovery might look like [7]. There has also been a surge in the number of pharmaceutical companies focused on making ready a safe and effective vaccine while testing pre-existing drugs that may mitigate or show positive significant effects on the COVID-19 virus [8]. More recently, there has been an average number of 123 million cases worldwide, with 69.8 million persons recovering and a mortality figure of 2.71 million. In Nigeria, a total of 162 thousand cases have been reported, with 148 thousand persons recovering, and 2030 deceased [8]. While human-to-human transmission of COVID-19 was confirmed in January 2020, it was first thought to occur via respiratory droplets from sneezes and coughs in ranges of about 1.8m with an average of 1000 SARS-CoV-2virions reported to initiate a new infection[9]. Furthermore, while the nasal cavity is the most prominent site for the infection which could be airborne, another possible means of contraction may be indirect contact via contaminated surfaces [9]. The virus remains viable on Plastic and Steel surfaces for about 72 hours but is not known to survive on paper for up to 24 hours [10].

2. Pathogenesis of corona virus disease

Causative virus for COVID-19 is called "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)" [11]. The specific surface protein that provides the entry door in human cells for both SARS-CoV and SARS-CoV-2 is Angiotensin-Converting Enzyme-2 (ACE-2)[9]. However, SARS-CoV-2 binds to Angiotensin Converting Enzyme-2 receptors with tenfold higher affinity, and as such, is far more transmissible than SARS-CoV [9]. Following transmission, Angiotensin Converting Enzyme-2 Protein, highly expressed in human cells like type-2 alveolar cells (AT^2), oral esophageal, myocardial, and urothelial cells among others, mediates internalization of SARS-CoV-2 to epithelial cells of the oral cavity and mucosal membranes of the conjunctiva [12]. Similar to SARS-CoV, SARS-CoV-2 binds and docks by a glycoprotein expression to the angiotensin converting enzyme-2 (ACE-2) and requires proteolytic activation by transmembrane protease serine 2 (TMPRSS2), and cathepsin B and L for maximum entry[13,14]. Cleavage of fusogenic transmembrane proteins such as furin and viral envelop glycoprotein by proteolytic enzymes is also essential to control viral cell entry, replication and infectivity[15, 16]. ACE-2 protein, which is a carboxy-peptidase responsible for the production of vasodilatory peptides and endothelia-dependent vasodilation facilitated by nitric oxide, are widely distributed in the respiratory tract epithelium, lung parenchyma cells, cardiovascular and gastrointestinal tissues[17]. Perhaps, this hetero-distribution may account for the diverse range of symptoms and multiple organ damage in many intensive care COVID-19 patients.

ACE-2 has an important role in inflammatory signaling pathways, hence there is a greater chance of tissue injury [18]. ACE-2 is expressed on type I and II alveolar epithelial cells in a normal human lung and the binding with SARS-CoV-2 provokes an elevated expression of this protein [19]. While expression of ACE-2 may be age dependent, limited studies suggest that ACE expression is reduced in females compared to males [9]. This may suggest the incidence of a higher number of Covid-19 cases in men compared to women. ACE-2 is a key element of the Renin-Angiotensin System (RAS) protective axis which is one of the major control systems for blood pressure and fluid balance [19]. The major biologically active hormone generated by this system, angiotensin II (Ang II), is produced by sequential cleavage of peptides derived from the substrate molecule angiotensinogen (Agt) [19]. By enzymatic reaction, angiotensinogen is converted into Angiotensin I (Ang I) through the action of renin, an aspartyl protease [19]. The generation of angiotensin II (Ang II) by the action of angiotensin-converting enzyme (ACE), the main effector of the system, induces an increased blood pressure, promoting vasoconstriction and inflammation [19]. This tends to throw more light on observed clinical features of Covid-19 disease such as hypokalemia, vasoconstriction, and a propensity for Acute Respiratory Distress Syndrome (ARDS) which usually presents as interstitial and alveolar pneumonia[20].

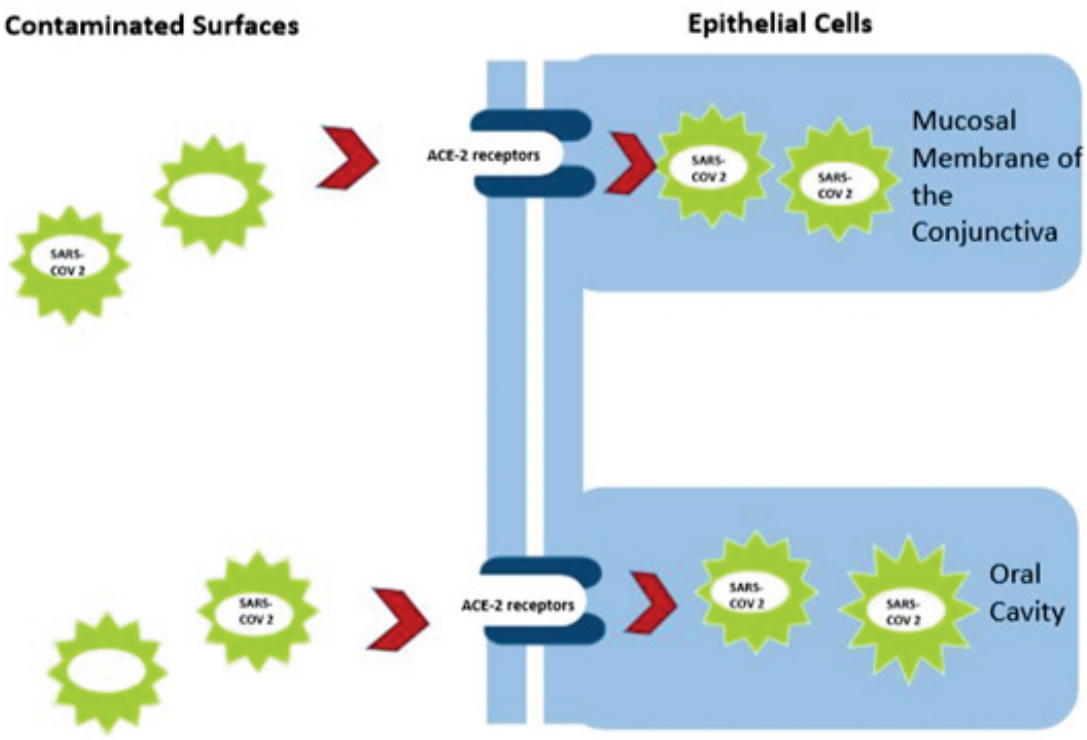

Figure 1: Diagram showing entry of SARS COV-2 from contaminated surfaces into human epithelial cells.

SARS-COV 2 (Severe Acute Respiratory Syndrome Coronavirus 2), ACE-2 (Angiotensin Converting Enzyme-2).

2.1 Inflammatory cascades in corona virus infection

Covid-19 infection is usually characterized by aggressive inflammatory responses, causing a release of large amounts of pro-inflammatory cytokines in an event known as "Cytokine Storm" which is also defined as a stern immunological response depicted by sudden extrusion chemical mediators of inflammation into the blood[21]. Severity of Covid-19 infection depends largely on the level of inflammatory cytokines such as Interleukins, Granulocyte Colony Stimulating Factor, IFN-Inducible Proteins, Monocyte Chemo-attractant Protein 1, and Tumor Necrosis Factor-alpha [21]. There is usually an observed reduction in lymphocytic cells ($CD4^+$ and $CD8^+$) and natural killer (NK) cells in Covid-19 virus infection, thereby facilitating deficits in immune responses [20].

After an inflammatory response, the hemostatic system is activated through endothelial dysfunction, platelet activation, and thrombo-inflammation [21]. Innate and adaptive immune responses are then stimulated, leading to activation of inflammasomes, consequently triggering endothelial cells to secrete pro-coagulating and anti-fibrinolytic factors; tissue factor (TF), von willebrand, thromboxane A_2, and tissue plasminogen activator-inhibitor 1[11]. On loss of vascular integrity, TF binds to factor VII and this in turn leads to coagulation, generating thrombin which converts fibrinogen to fibrin [11]. A major mechanism through which coagulating factors increase inflammation is by binding to receptors activated by proteases and protease activated receptors (PAR) [11].

One of the end results of chronic inflammatory reactions in coronavirus infection induced by a variety of stimuli including persistent infections, autoimmune reactions, allergic responses, chemical insults, radiation, and tissue injury is fibrosis, which is usually characterized by lesions on the lungs or pulmonary tissues [21]. Inflammatory mediators such as interleukins-13 and 21, caspases, tumor growth factors, angiogenic factors, acute phase proteins (SAP), and components of the renin–angiotensin–aldosterone system have been identified as important regulators of fibrosis[11].

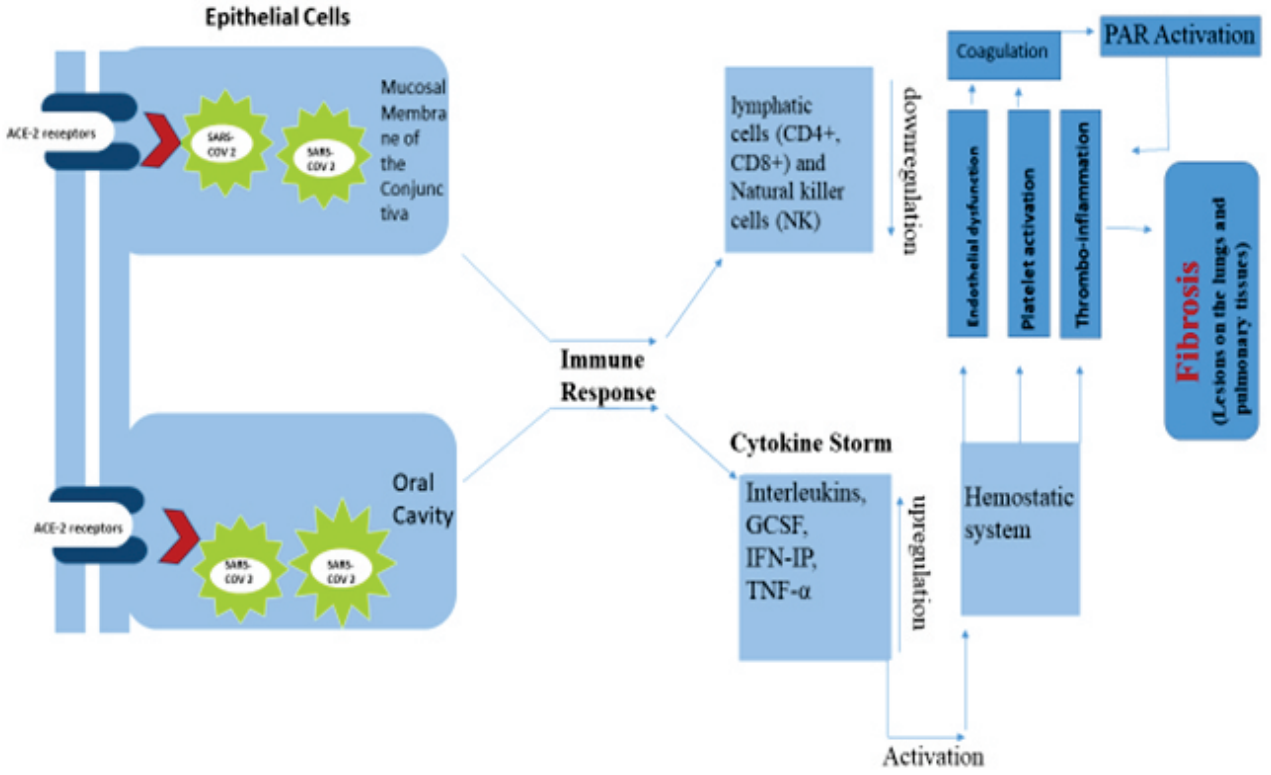

Figure 2: Schematic diagram illustrating thrombo-inflammatory cascades in Covid-19 virus disease.

Cd^{4+}/ CD^{8+} (Cluster of differentiation), NK (Natural Killer Cells), GCSF (Granulocyte Colony Stimulating Factor), IFN-IP (Interferon Inducible Protein), TNF-a (Tumor Necrosis Factor Alpha), PAR (Protease Activated Receptor), ACE-2 (Angiotensin Converting Enzyme-2), SARS-COV 2 (Severe Acute Respiratory Syndrome Coronavirus 2).

2.2 Novel role for dexamethasone in a pandemic era

Presently, while there may be no specific cure for Covid-19, the scientific community has recorded significant progress with respect to testing or screening pre-existing drug molecules that could ameliorate the effects of covid-19 induced pathological derangements [22]. Dexamethasone, azithromycin, lopinavir/ ritonavir, hydroxychloroquine, chloroquine and ivermectin, have all been reported to show promising results against the covid-19 virus [22]. Moreover, as drug therapy remains a cornerstone in the clinical management of COVID-19, the importance of other supportive care, which may include treatment to relieve symptoms, fluid therapy, oxygen support, prone positioning as needed, and devices to support other affected vital organs remains imperative to effective management of coronavirus-infected patients [23].Dexamethasone which was introduced for medical use in 1958 was however first synthesized in the laboratory in 1957 by Philip Showalter Hench [24]. Having been discovered as an anti-inflammatory steroid and marketed as "Decadron" in 1959, its evolution in the market in 1959, has led to it now popularly being used by medical professionals in severe covid-19 patients to relieve symptoms of Pneumonia [24]. It is a synthetic glucocorticoid with marked anti-inflammatory and immunosuppressant activities [25]. Although it is a commonly used drug, it's mechanism of action is quite unclear as studies suggest it acts majorly by inhibiting and suppressing inflammatory cells and mediators, resulting to decreased leucocyte migration to the site of inflammation, as well as neutrophil apoptosis[26]. In addition, there is also significant inhibition of phospholipase A_2, leading to a decrease in formation of arachidonic acid and other inflammatory transcription factors [25]. Absorption of dexamethasone via intramuscular route is slower than intravenous route and bioavailability through oral administration is approximately 60-70% with a plasma protein bound estimate of 77% in healthy subjects[26]. The drug is 6-hydroxylated by CYP3A4 to 6α and 6β hydroxyl-dexamethasone, with <10% eliminated in urine while half-life is about 4 hours [25].In addition, chronic high doses of dexamethasone may be associated with development of cataracts, glaucoma, hypertension, hyperlipidemia, pancreatitis, myopathy, osteoporosis, mood changes[27]. It may also cause decreased resistance to infections, moon face, hyperglycemia, hypocalcemia, metabolic acidosis,

growth suppression, acne, dermal atrophy, and secondary adrenal insufficiency[27]. Some of its clinical indications include arthritis, blood/ hormone disorders, allergic reactions, skin disease, eye problems, breathing problems, bowel disorders, cancer, immune system disorders, asthma, and edema amongst others [28]. Doses ranging from 0.4-10mg daily (depending on the severity of the disease) can be administered in the management of most chronic inflammatory disorders in humans[29], whereas for the treatment of severe Covid-19 virus infection, the world health organization in 2020 recommends a regimen of 6mg daily dose for seven days. However, the least possible dose within the stipulated range should be adopted to achieve the same therapeutic goals[29].

Dexamethasone remains one of the clinical agents that has shown positive effects in the treatment of Covid-19 [29]. However, this contradicts what scientists had previously reported on the use of corticosteroids in the management of other forms of coronavirus (MERSr-CoV and SARSr-CoV) that had earlier emerged [30]. It was shown in most studies that corticosteroid use had no beneficial effects on mortality rate or survival span of hospitalized infected patients [30]. Nonetheless, the present SARSr-CoV-2 pandemic appears to have unveiled new insights on glucocorticoid use as recent research has brought to limelight the effects of dexamethasone and other related steroids in attenuating inflammation induced perturbations in Covid-19 viral infection [30]. Notwithstanding, this seemingly advantageous outcome of dexamethasone use in Covid-19 is directed to a sub class of patients, as it was proclaimed that Dexamethasone use in patients on mechanical ventilation or other forms of supportive therapy showed better recovery cycle with respect to a reduction in mortality rate and severity of disease condition [30]. An interesting uncovering on the choice of steroid use in Covid-19 bothers on the assumption that therapeutic responsiveness positively correlates with severity of disease [30].

3. Conclusion

While the use of dexamethasone in the management of COVID-19 patients is encouraged in certain justifiable instances by the Medical and Scientific Community, a lot remains to be explored on how this old drug mitigates the effects of a new disease. Novelty and complexity of the covid-19 virus may contribute to hindrances and challenges in coming up with effective drug therapy to treat the disease. However, better understanding of the multifaceted nature of the virus and viral pathology in humans will foster the development of novel or pre-existing therapeutic agents to combat the COVID-19 infection. In addition, while it is not fully known which of the multiple pharmacological mechanisms of dexamethasone's action is responsible for its effect on the covid-19 virus, scientists have suggested inflammation or immune-inflammatory pathways to be the potential and pivotal target towards the COVID-19 virus disease. Conversely, future studies hope to streamline or articulate more specific biomarkers that relate covid-19 Virus with inflammation. This would consequently pose as an invaluable tool for developing better and safer drugs/biological agents that may alleviate and cure corona virus infection.

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