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Research Article

Corticosteroid Actions on COVID-19 and SARS Viral Immune Pathology; A Review Article

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Abstract

Only few studies are available to evaluate the effectiveness of corticosteroids in SARS and SARS-CoV-2. Corticosteroids is a hormone, as well as a drug, having therapeutic levels and lethal doses, so needs to balance the doses accordingly to the disease. Here we discuss the use of steroids in SARS, MERS and COVID-19 with reviewing the pharmacological and immunological basis of steroids in virus pathology. Steroids can be beneficial in these viral infections by suppressing SARS-CoV induced antibodies, T cells, B cells, cytokines, chemokines, complement signaling, antibody-dependent enhancement, vascular and hematological manifestations, viral replication and COX-2/PGE2 pathways. Steroids can also protects against cell apoptosis and enhance tissue recovery. Corticosteroids have shown some favorable outcomes in patients with SARS and COVID-19 but delayed viral clearance and secondary infections have been reported. Currently it is difficult to formulate clear recommendations regarding steroid use in COVID-19 but can be used in selected patients.

Keywords: SARS coV; SARS co V-2; Corticosteroids

Abbreviations

COVID -19: Corona Virus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Corona virus-2; WHO: World Health Organization; ARDS: Acute Respiratory Distress Syndrome; MERS-CoV: Middle East Respiratory Syndrome - Corona Virus; SARS-CoV: Severe Acute Respiratory Syndrome - Corona Virus; ALI: Acute Lung Injury; ACE2: Angiotensin-converting Enzyme 2; IL: Interleukin; CD209L: Human Cluster of Differentiation209; L-SIGN: Liver/lymph Node-Specific Intercellular Adhesion Molecule-3-grabbing integrin; DC-SIGNR: Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin related; DC-SIGN: Dendritic Cell-Specific Intercellular Adhesion Molecule-3-Grabbing Non-integrin; DAD: Diffuse Alveolar Damage; MCP-1: Monocyte Chemo Attractant Protein 1; IP-10: IFN-gamma-inducible Protein-10; TNF-α:

Tumor Necrosis Factor Alpha; GCSF: Granulocyte-colony Stimulating Factor; MIP1 α: Macrophage Inflammatory Proteins 1 Alpha; FcγR: Fc-gamma Receptors; COX-2: Cyclooxygenase-2; PGE: Prostaglandin E; HAT: Human Airway Trypsin-like Protease; TGF- β1: Transforming Growth factor-β1

Introduction

Corona virus disease 2019/COVID -19, caused by Severe Acute Respiratory Syndrome Corona virus-2 (SARS-CoV-2), started in the Chinese city of Wuhan (Hubei province) [1]. It is currently spreading as a pandemic across the world and World Health Organization (WHO) declared this as a global health emergency. Clinical presentation of COVID -19 range from mild to severe disease [uncomplicated illness, mild pneumonia, severe pneumonia, Acute Respiratory Distress Syndrome (ARDS) [2,3]. Although most human coronavirus infections are usually mild or asymptomatic and recover without complications, two epidemics of the two beta coronaviruses; Severe Acute Respiratory Syndrome- corona virus (SARS-CoV) [4] and Middle East Respiratory Syndrome - corona virus (MERS-CoV) [5] have caused epidemics, with mortality rates of 10% and 37% respectively [2]. Recent outbreaks of these emerging viruses, emphasize the need to characterize the mechanisms responsible for virus-mediated acute lung injury (ALI) and ARDS [6]. SARS-CoV-2 shares almost 80% of the genome with SARS-CoV [7] and is similar to the coronavirus responsible for severe acute respiratory syndrome (SARS), a member of the subgenus Sarbecovirus (Beta-CoV lineage B), but it is more distant to the coronavirus responsible for Middle East respiratory syndrome (MERS), a member of the Merbecovirus subgenus (only 50% homology with SARS-Cov-2) [5,8].

The American College of Critical Care Medicine issued a recommendation that glucocorticoids should be considered in the management of severe ARDS [12]. The advantages and disadvantage of administration of corticosteroids in viral fever have been studied and data suggest increased mortality and secondary infection rates in influenza infection, impaired clearance of SARS-CoV and MERS-CoV and complications of corticosteroid therapy in survivors [9,10,13]. Patients with SARS had no survival benefit and possible harms (avascular necrosis, psychosis, diabetes, and delayed viral clearance) [11] with steroids. However in a study on corticosteroids in H1N1 pandemic in 2009-related critical illness, there was no significant association between corticosteroids and mortality after adjusting for time-dependent differences [14]. It was suggested that that patients with COVID-19 infection will not benefit from corticosteroids and there might be harmful effects with such treatment [15].

Currently, as in dengue fever, World Health Organization does not recommend routine use of corticosteroids in treatment of COVID-19. However after considering the immunopathology, it has been shown that corticosteroids can be effective, if used cautiously in dengue with sustained therapeutic blood levels of corticosteroids for an adequate duration within a therapeutic window [16]. Corticosteroids is a hormone, as well as a drug with a therapeutic level as well as lethal dose, so is necessary to balance and adjust the doses accordingly to the disease and it's immunological actions. If steroids are not administrated cautiously, there will be harmful effects and increased motility and morbidity and inappropriate administration of corticosteroids in viral fevers can be the cause for lack of benefits [16]. On this basis, it can be assumed that in selected patients steroids might have a place in COVID-19 infection as well. In this review we will discuss the pathology and steroid use in SARS, MERS and COVID-19 and since these viruses have similar features [17] and genomes we can assume that viral immunopathology and effects of steroids can be similar in these infections.

Methods

We used multiple search strategies to retrieve all published articles on steroid use SARS, MERS and COVID-19. We searched Pubmed and Google Scholar, using the search terms; "Covid19", "SARS-CoV2", "SARS-CoV", "MERS-CoV", "Corticosteroids", "steroids", "Pathology", "Immunology", "Acute respiratory response syndrome". We also scanned multiple news sources on Google for relevant publications.

Results

We analyzed 99 articles directly and indirectly related to corticosteroids and COVID-19 and results are divided according to topics.

Pathology and histopathology of SARS and COVID19

The pathogenesis of SARS is complex and multiple factors lead to severe injury in the lungs and viral dissemination to several other organs. The SARS coronavirus infect the epithelial cells of the respiratory tract and cause diffuse alveolar damage and several other organs/cell types may be infected in the course of the illness, including intestinal mucosal cells, tubular epithelial cells of the kidneys, neurons and immune cells [18]. SARS-CoV enters the epithelium of the respiratory tract via *Angiotensin-converting enzyme 2* (ACE2) [19], which is expressed abundantly on the luminal surface of tracheobronchial and alveolar epithelium [20]. In addition it was proposed several working modes of functional receptors for SARS-CoV-2, including monomer receptor, homodimer receptor, alternative receptors, co-receptors and transmissive receptor. Moreover in addition to ACE2 protein is express in the lung it was found in various organs, including oral and nasal mucosa, nasopharynx, stomach, small intestine, colon, skin (conjunctiva, facial skin), lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain (100) and eye (on the surface of the eye (e.g., conjunctiva and cornea), inside the eye (trabecular meshwork, aqueous humor, iris, ciliary body, non-pigmented ciliary epithelium, and retina) [101].

After this the virus replicates in the upper respiratory tract [21]. Human Cluster of Differentiation209 (CD209L) (also called Liver/lymph node-specific intercellular adhesion molecule-3-grabbing integrin (L-SIGN)), a C-type lectin in human lung in type II alveolar cells and endothelial cells is also a potential target for SARS-CoV. Several other viruses (Ebola and Sindbis) also use this as the functional receptor [23]. The lectins, Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN) and Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin related (DC-SIGNR) are involved in viral infection and viral dissemination [24]. DC-SIGN is the receptor for the entry of dengue virus as well and are expressed on type II pneumocytes, endothelial cells, certain types of dendritic cells and alveolar macrophages [25,26]. ACE2 is a protective against acute lung failure and lung edema and SARS-CoV infections and the Spike protein of the SARS-CoV cause ACE2 and this down regulation contributes to lung injury [27]. SARS-CoV-induced epithelial cytokines, such as Interleukin-6 (IL-6) and Interleukin-8 (IL-8) can also rarely cause a life-threatening respiratory disease [22]. When ACE2 is concerned again it is a protective against acute sever lung failure and lung edema [28]. Moreover Angiotensin I and angiotensin II have been associated with inflammation, oxidative stress, and fibrosis, and ACE2 is involved in their deactivation [29]. If overwhelming coronavirus infection, with binding to ACE2 on epithelial targets leading to down regulation of the receptors [27] and this down regulation contributes to lung injury. This occurs not only in the lung but in other tissues expressing these ACE2 proteins, including the kidney, intestines, and brain. Thus availability angiotensin II increases and it could lead to reactive oxygen species formation and interference with antioxidant and vasodilatory signals such as NOX2 and eNOS [38]. This causes to loss of autovasoconstriction and regulation of lung blood flow through injured vascular segments. Finally the pathology contribute to further activation of compliment proteins and increases shunting and severe hypoxemia to the organs and tissues [27] (Figure 1). Interestingly glucocorticoids are a type of ACE2 activator that may play a protective role in the respiratory and digestive systems by activating ACE2 and suppressing cytokine storm. Among glucocorticoids hydrocortisone showed the strongest effect on ACE2 activation, followed by prednisolone, dexamethasone, and methylprednisolone. Thus it can be assumed that hydrocortisone may not good for early phase due to high viral entry and in middle phase due to impair lung function by water retention ability of the drug. Other drug, dexamethasone, and methylprednisolone have been mainly used in many clinical trials that may be suggested to preserve protective important immune modulatory action of ACE2 against dysfunction immunopathology and minimize level of viral entry through ACE2.

Steroids actions in viral pathology

Steroids stop SARS-CoV induced antibodies and its actions

Antibodies against SARS-CoV nucleocapsid (N) protein, spike (S) protein and nonstructural protein 3a have been detected in SARS cases [31]. In recovered patients these antibodies titers are higher and levels develop slowly but maintained for a longer period, compared to patients who died. At the same time antibodies developed faster but diminished rapidly in deceased patients compared to recovered patients. So this large and quick immune response might have triggered a detrimental immune reaction in deceased patients [32]. Anti-spike IgG promote production of monocyte chemo attractant protein 1(MCP-1) and IL-8, proinflammatory monocyte/macrophage recruitment and accumulation, which cause severe acute lung injury [33]. Autoantibodies against pulmonary epithelial cells and endothelial cells in these patients cause cytotoxic injury, post-infectious cellular injury and trigger systemic vasculitis [34,35]. It can be assumed that blockade of these antibodies in SARS-CoV infection by corticosteroids can reduce pro inflammatory cytokine production and sever lung injury (Figure 1).

Steroids suppress T cells, B cells, cytokines and chemokines in corona viral pathology

In SARS patients Th1 cytokine (interferon gamma), inflammatory cytokines (IL-1, IL-6 and IL-12), neutrophil chemokine (IL-8), MCP-1 and Th1 chemokine IFN-gamma-inducible protein-10 (IP-10) were significantly elevated due to the activation of Th1 cell-mediated immunity, monocytes/macrophages,neutrophils and hyperinnate inflammatory response (Figure 1). This leads to pulmonary inflammation and extensive lung damage [36]. MERS-CoV

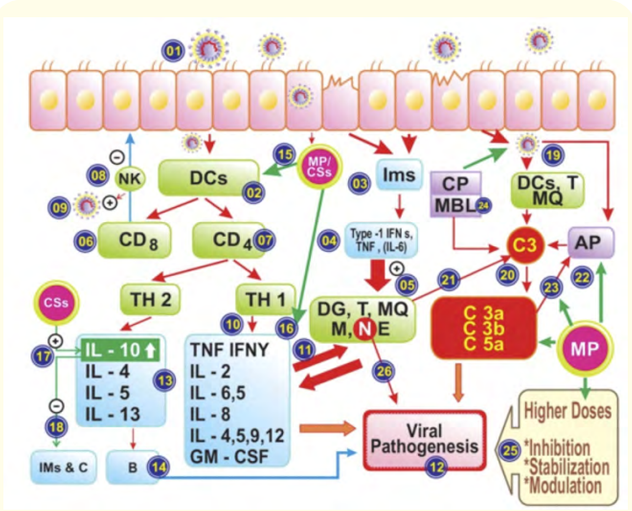

Figure 1 : Viral infection and activation of immune cells causing lung pathology and steroids counteracting the steps.

Virus (1) infect respiratory epithelial cells and then (2) dendritic cells (DCs). The-virus infected epithelial cells release immune mediators (3) type -1 IFN s, TNF, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), granulocyte colony stimulating factor (G-CSF), and granulocyte macrophage-CSF (GM-CSF)(4). The type I IFNs can also directly activate immune cells (IMs) and indirectly initiate immune responses (5) The infected and type -1 IFN s induced DCs or antigen presenting cells (2) activate CD8 (6) and CD4 T(7). CD8+ cells matured into NK cells that help in controlling early viral infection (8) but the intense proliferation of CD8+ cells can also contribute to increase viral pathogenesis (09). Activated Type 1T helper (Th1) cells produce interferon-gamma (IFN γ) interleukin (IL)-2, and the tumor necrosis factor (TNF)-beta (10), which activates macrophages (11) to release immune mediators in RVSs pathology (12). Activated type 2 Th (Th2) cells produce IL-4, IL-5, IL-10 and IL-13, (13) which are mainly responsible for antibody production through B cells (14). Methyl prednisolone (MP) usually prevents DC differentiation and maturation(15) CSs further involve in the inhibition of the release of pro-inflammatory cytokines IL-1 α and beta, IL-2, IFN γ and TNF- α, (16) and up-regulation of the anti-inflammatory cytokine IL-10(17) IL-10 induced by Th2 or CSs or both contribute to inhibition of several macrophage functions and other inflammatory molecules (18). RVSs infect both DCs and T-cells (19) and up-regulate C3a and C5a receptors and produce C3 peptide (20). Viral infected macrophage also involve in C3 peptide production (21). MP directly inhibits the alternative (22) and amplification pathway (23) of the complement but not the MBL path way and classical pathway (24). CSs in higher doses may function by regulating multiple events in the immunological apparatus including inhibition of compliments, stabilization of membranes and modulation of vivo components level s(25) halting sever life threatening pathogenesis. Neutrophils can form and release neutrophil extracellular traps (NETs) that may also damage respiratory epithelium and endothelium possibly by exposure to hydrolytic enzymes and cytotoxic proteins (26) that have been associated with more severe lung pathology (12) during viral infection.

infection was associated with increased concentrations of interferon gamma, Tumor necrosis factor alpha (TNF-α), IL-15 and IL-17 [37]. Patients with COVID-19 also had high levels of IL1B, interferon gamma, IP10, and MCP1. Patients with sever COVID-19 infection had higher concentrations of Granulocyte-colony stimulating factor (GCSF), IP10, MCP1, Macrophage Inflammatory Proteins 1 alpha (MIP1 α), and TNFα [38].

Glucocorticoids can reduce the activity of T cells, inhibit cytokines and reduce inflammation and lung damage [39,40]. Corticosteroids reduce IL-8, MCP-1 and IP-10 concentrations significantly [36]. Methyl prednisolone inhibits induction of primary T and B cells and the release of pro-inflammatory cytokines interleukin-1, interleukin-2, interferon- gamma, TNF-α, and interferon-alpha [41,42,46]. It also up-regulates anti-inflammatory cytokine IL-10 [43]. IL-10 reduce inflammatory responses by reducing cytokines [44]. Hydrocortisone can significantly decrease endotoxin induced expression of TNF–α, IL-6, IL-8 and IL-1 and reduce inflammatory cytokines without impairing innate immune responses necessary to combat bacterial infections [45]. Moreover steroids alter the functions of neutrophils, eosinophils, mast cells and endothelial cells [47]. Dexamethasone also augment FcγRIIb protein expression significantly, which inturn reduce immune responses, autoimmunity, proinflammatory chemokines and cytokines [48]. [Fc-gamma receptors are divided into activating and inhibitory receptors and activating Fc-gamma receptors (FcγRI, FcγRIIA, and FcγRIII) triggers production of proinflammatory chemokines and cytokines whereas the inhibitory Fc-gamma receptors (FcγRIIB) counteracts activating FcγR [49].

Steroids inhibit complement signaling of coronavirus infection

Following viral infections, both dendritic cells and T-cells up-regulate C3a and C5a receptors and production of C3 peptide. In patients with severe viral infections (e,g dengue), large amounts of C3a increase recruitment of monocytes, macrophages and dendritic cells, vasodilatation, permeability of small blood vessels, disrupt vasculature and smooth muscle contraction [50,51] (Figure 1). Due to compliment activation, it was said that coagulation pathways were affected in in COVID-19 immunopathology [38,102]. This leads to micro vascular compliment protein deposition in blood vessels wall, sever inflammatory reaction, micro vascular injury and thrombosis [38,104]. This latter effect has been identified to the cause of sever pathology of COVID-19 infection and death [102]. These complements induce generation of cytotoxic oxygen free radicals, mediate chemotaxis, degranulation and release of histamine from basophils, neutrophils, eosinophils and mast cells, initiate a cytokine storm and contribute to ALI [51]. C3a, C5a and C5b-9 cause cardiovascular collapse, similar to an IgE mediated allergic response [52]. Thus, higher complement levels correlate with the disease severity of viral illness [53]. Increased complement pro-

teins, complement receptors and C proteins create a positive feedback loop that can lead to a systemic proinflammatory response in SARS coV patients [54]. In one study, complement deficient mice with SARS had reduced neutrophils in their lungs and inflammation [54].

In dengue, it is observed that methyl prednesolone inhibits the pathway and amplification of complements [55]. Moreover, steroids in higher doses stabilize membranes and inhibit complements, which reduce histamine release, vascular permeability and circulatory collapse [47,56]. This suggests that inhibition of complements with steroids might be effective to reduce inflammatory damage in SARS.

Steroids reduce Antibody-dependent enhancement

SARS-CoV causes maturation of dendritic cells *in vitro* [57] and mature of dendritic cells facilitate antibody dependent enhancement via FcγIIa and FcγIIb receptors [58]. Antibody-dependent enhancement has also been observed in corona viruses, where antibodies facilitate viral entry and enhance viral infection in host cells [59]. Virus use this mechanism to infect macrophages and this can turn a normal mild viral infection to into a life-threatening infection [60]. Glucocorticoids down regulate dendritic cell differentiation and maturation [61]. When dendritic cells fail to mature with steroid administration, they will fail to stimulate T-cells and will reduce the antibody-dependent enhancement induced rapid viral dissemination [46].

Steroids suppress Vascular and hematological manifestations in SARS

Pathology in SARS co V and SARS co V-2 is mainly focused to respiratory system, but hematological and vascular manifestation could be observed in sever diseases stage [62]. Haemorrage has also been observed in SARS co V as well [63]. MCP-1, which is elevated in SARS [36] and COVID-19 [38], can increase the permeability by disruting tight junctions of human vascular endothelium cells in dengue fever [64]. Corticosteroid can reduce MCP-1 and other cytokines involved in this endothelial permeabilty [36] (Figure 2).

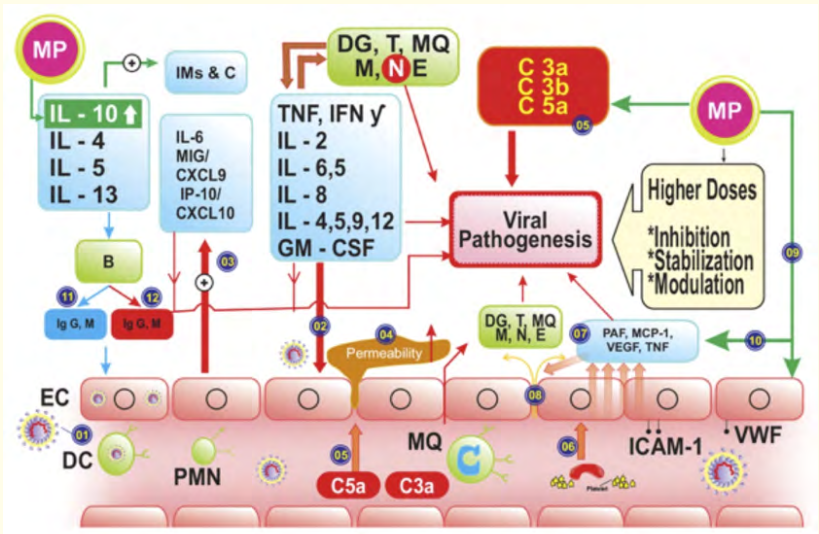

Figure 2: Viral infection causing activation of immune cells leading to hematological manifestations.

Damage to alveolar epithelium can expose and increase the susceptibility of localized endothelium to injury directly by virus (01) and indirectly by immune mediators (02). Then it releases Pro inflammatory cytokines and chemokines such as Interleukin- 6 (IL-6), Chemokine (C-X-C motif) ligand 9/ monokine induced by gamma interferon (MIG/CXCL9), C-X-C motif chemokine 10/ Interferon gamma-induced protein 10 (IP-10/CXCL10) in response to a virus infection (03) leading to increased vascular permeability and edema (04). Release of pro inflammatory cytokines disrupt the integrity of the endothelial-epithelial barrier and leukocytes can enhance endothelial permeability (04). Moreover complement molecules and enzymes (C3a and C5a) (05) induce oxidative bursts, cytotoxic oxygen radicals, chemotaxis and inflammation. Activation of platelets (06), complements (05) and release of inflammatory mediators such as Platelet activating factor (PAF), monocyte chemoattractant protein-1 (MCP-1), Vascular endothelial growth factor (VEGF) and tumor necrosis factor (TNF) (07) lead to plasma leakage (08) and contribute to the development of vasculopathy. Methyl prednisolone (MP) stabilizes endothelium (09), reduce production of prostanoids, NO and COX-2 which are the permeability facilitators of VEGF and TNF respectively (10). MP also reduces antibody production, which can damage endothemium [11,12].

Steroids reduce Cyclooxygenase-2 (COX-2), Prostaglandin E (PGE) activity and viral replication

Cyclooxygenase-2 (COX-2) and Prostaglandin E (PGE) activity is important for the replication of several viruses and cytokines from viral infected cells increase COX-2/PGE production as well [66-68]. However the role of COX activity in corona viral replication has not been explored [65], but PGE2 levels were high in SARS patients suggesting a relationship between COXs and PGs in corona viral pathogenesis [69]. It has been shown that S protein of SARS-CoV induces COX-2 and this cause pulmonary inflammation and immune hyperactivity [70]. Steroids are potent inhibitor of COX-2 and PGE2 [71]. Thus, it could be suggested that steroids contribute indirectly to reduce viral pathogenesis by COX-2/PGE2 pathways and can be suggested to use CSs vey early in the cause illness before viremia taken place. However "Early" hydrocortisone treatment (initiated in <7 days of illness/viral replication phase) was associated with high plasma viral levels and prolong duration of viraemia [72]. This may be associated with administration of water retention steroids to the patients who are in risk of sever lung pathology. In addition steroids without water retention ability can be used and are clinically practiced in later course of the disease (e.g. in the second week following clinical deterioration), when the viral load is low and excessive immune response causing lung damage [72]. Moreover the Human Airway Trypsinlike protease (HAT) and PGE-2 contribute to reduce fibrosis in pulmonary fibrosis so

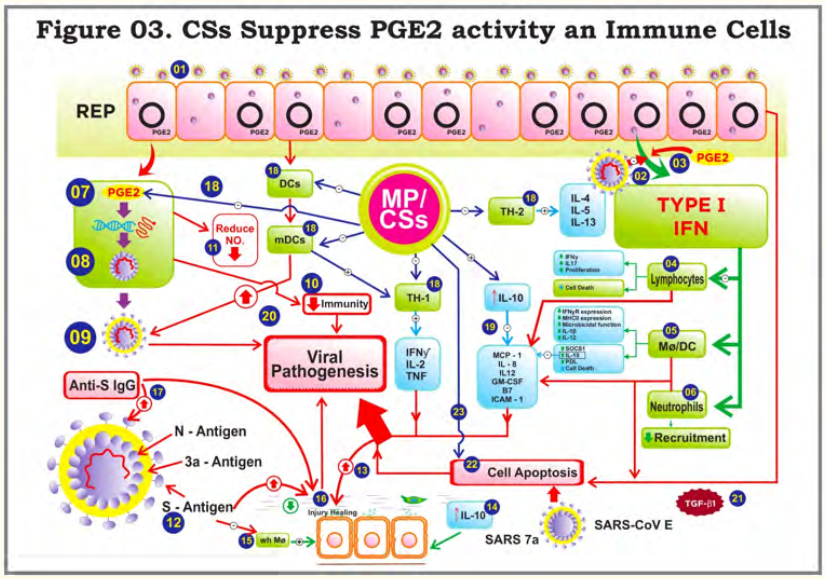

Figure 3: CSs contribute to have antiviral actions and facilitate resolution of wound healing restores homeostasis.

Coronaviruses (01) causing SARDS and COVID19 that inhibit Type one IFMNs producing innate antiviral responses (02) in the infected cells . Type one IFMNs suppress lymphocyte reducing IL-17,IFN gamma leading to increase cell death and reduce viral proliferation (4) .Macrophage and dendritic cells are also suppressed and These lead to reduce IL-12,1L-1 ,beta IFN yR expression and reduce microcidal function ,MHCL II expression increase SOCS 1, IL -10 ,infected cell death and PDL- 1 (5) .Type one IFMNs also suppress recruitment of Neutrophil. (06) Respiratory epithelial cells and immune cells have a signaling via Toll-like receptors for viral entry. Thereafter the viruses induce a strong pro-inflammatory cytokine response that is associated with immunopathology of SARDS and COVID -19 That leads to significant morbidity and mortality of fatal viral illnesses . Increased PGE-2 in viral infected cells (7) can play a major role in the viral infection directly by stimulating viral gene expression and replication(8) and increasing the production and release of virions (9). The host immune system can be modulated by PGE2, with regards to immunosuppression (10), inhibition of nitrogen oxide (NO) production (11), inhibition of interferon (IFN) action (03) and increasing apoptotic pathways. CSs/MP reduce the elevated expression of COX-2and then suppress expression of Prostaglandin E2 (PGE2) (7-18) that is an eicosanoid generated by cyclooxygenase. Spike Antigen of SARS coV (12) impair wound healing. Immune markers (13) induce implication and recruitment and accumulation of macrophage lead you to impair tissue healing(16). IL-10 induced by CSs/MP and Type one IFMNs (14) facilitate resolution of wound healing restores homeostasis. (15)Wound healing macrophage facilitate wound healing activity process. (16)Impairment of wound healing increased viral pathogenesis. Anti-S Ig G produced against Spike (s) protein of SARS CoVirus (17) and damage lung epithelium. CSs/MP contribute to supers excess stimulation of immunological process by inhibiting production of PGE2,suppressing immune cell such as TH-1,TH-2 leading reduced antibody induced pathology and , DCs ,m DCs (18) that are involving sever viral pathology . Moreover it contributes to enhance IL-10 (19) and finally reduce and suppress the pathogenesis (20) of viral immune pathology. (TGF-β1) (21) produced due to epithelial cell injury has important roles in lung fibrosis and the potential to induce apoptosis in several types of cells .In addition SARS-CoV 7a and E, contribute to undergo intrinsic apoptosis (21). CSs/MP contribute to suppress the apoptosis(23).MP-methyl prednisolone. CSs-corticosteroids. DCs-dendritic cells. M DCs-mature dendritic cells.

continuous. Therefore It is suggested that steroids should be used in later course of the disease (e.g. in the second week following clinical deterioration), when the viral load is low and excessive immune response causing lung damage [72]. The Human Airway Trypsin-like protease (HAT) and PGE-2 contribute to reduce fibrosis in pulmonary fibrosis so continuous persistent high doses of steroids that reduce PGE-2 levels can lead to more fibrosis rather than recovery [73]. Therefore tapering techniques in late stages can also be recommended.

Steroids protects against cell apoptosis

SARS-CoV structural proteins can trigger apoptosis *in vitro* [74]. SARS-CoV 7a induces apoptosis in the liver, kidney and lungs [75] and SARS-CoV E proteins in T-cell [74], thyroid glands, spermatogenetic cells, epithelial cells, pneumocytes, monocytes/macrophages and hepatocytes [76,77]. Viral infected alveolar and bronchial epithelial cells produce Transforming growth factor-β1 (TGF- β1), which can cause Fas-mediated apoptosis in lungs [78]. Thus, cells exposed to TGF- β1, SARS-CoV 7a and SARS-CoV E may undergo apoptosis and this apoptosis contribute to lung injury. Glucocorticoids can suppress apoptosis of cells like glomerular endothelial cells by multiple mechanisms [79]. In dengue fever, antibodies against dengue virus nonstructural protein 1 increase NO production by inducing NO synthase and NO results in endothelial cell apoptosis. Corticosteroids can inhibit Inducible Nitric Oxide Synthase [80] and so we can assume that steroids can be protective against cell apoptosis in viral infections (Figure 1 and 2).

Steroids enhance tissue recovery via IL-10

Anti-inflammatory cytokine IL-10 promotes epithelial wound healing and restore mucosal homeostasis [81] and corticosteroids enhances IL-10 production [43,82]. Thus, corticosteroids promote tissue recovery following viral infections via IL-10 and its anti inflammatory action [43,82].

Steroids strengthen of respiratory epithelium barrier

The bronchial epithelium forms the first continuous physical barrier to microbial infections and is part of the innate immune response. Some viruses, like adeno viruses, disrupt junctional integrity of human airway epithelia, allowing virus to enter and escape across epithelial barriers to the environment [106]. In addition it was provided evidences of a strengthened binding of SARS-CoV-2 E protein with the tight junction-associated PALS1 protein that is a cellular protein involved in maintaining tight junctions between epithelial cell [107]. It also interactions between the SARS E protein and PALS1 disrupt tight junctions promoting virus spread [107]. Claudins, occludin and junctional adhesion molecules (JAMs) are major constituent proteins of TJs and steroid treatment has been shown to improve epithelial barrier integrity, increase trans epithelial resistance and lead to a more integrated expression of the TJ proteins, occludin and ZO-1 [108]. Both budesonide and fluticasone have shown to efficiently control epithelial pro-inflammatory responses and barrier function upon mimicry of viral infection also. So we can assume that steroids can strengthen the physical barrier against the viral entry and then their replication.

Steroids in ARDS

In a study, Methylprednisolone (2 mg/kg per day) was given for 32 days to patients with unresolving ARDS and it showed an improvement in lung injury, Multiple Organ Dysfunction Score and reduced mortality [83]. However in another study, patients with established ARDS, high-dose methylprednisolone had no effect on the outcome [84]. Favorable result were evident for the use of corticosteroids in ARDS by decreasing the mortality with associated slight risk of infectious complications in a meta analysis in 2014 [85]. However in another meta analysis, the favorable effects of corticosteroid on mortality in ARDS were not seen [86]. Thus, steroid treatment in ARDS remains controversial.

Steroids in SARS and MERS

Corticosteroids have been used in SARS patients with a favorable outcome in some studies. In Hong Kong, corticosteroid (prednisolone 1 mg per kilogram of body weight per day) with ribavirin was given to patients with fever and leukopenia, thrombocytopenia. Patients with persistent fever and worsening lung shadowa were given an additional two or three pulses of 0.5 g of methylprednisolone daily as well. The majority in this study responded to this with resolution of fever and lung shadows [87]. In a another study, initial use of pulse methylprednisolone (methylprednisolone $\geqslant$ 500 mg/day) were more efficacious and safe compared to lower dosage

(methylprednisolone < 500 mg/day). This study recommended pulse methylprednisolone as the preferred steroid therapy in SARS [88]. Combined immunoglobulin and methylprednisolone daily for 3 days had shown a trend toward earlier recovery [89]. Early use of high-dose steroids in combination with a quinolone plus azithromycin has also shown favourable outcome, with clinical improvement, reduction in ARDS, mechanical ventilation and mortality in SARS [90].

In some case series, steroids have failed to show any therapeutic benefits [91,92]. It was also shown that early (<7 days of illness) corticosteroid (hydrocortisone) treatment was associated with a high plasma viral levels in both SARS [72] and MERS [93]. One patient with SARS has also died of aspergillosis with prolonged use corticosteroids [10]. One meta analysis concluded that corticosteroids in SARS patients had led to worsening of pulmonary disease or progressing shadows on chest X-rays and stated that clear recommendations cannot be made regarding corticosteroids use in SARS [11].

Steroids in COVID-19

Twenty six patients who received intravenous methylprednisolone (1-2mg/kg/d for 5-7 days) had a quick improvement of oxygen saturation and chest CT compared to patients without methylprednisolone [94]. In a descriptive study in china, 10 COVID-19 patients, who received short-term moderate-dose of corticosteroids (160mg/d) plus immunoglobulin (20g/d) after continued deterioration following low-dose corticosteroid (40-80mg/d) and immunoglobulin (10g/d) showed clinical (APACHE II score, oxygenation index, fever), hematological (lymphocyte count), biochemical (lactate dehydrogenase levels, C-reactive protein) and radiological (lesions in CT chest) improvement. This concluded that short-term moderate-dose corticosteroid plus immunoglobulin can be beneficial for COVID-19 patients who continue to deteriorate after the low-dose therapy [95]. Shang J and colleges suggested that corticosteroid therapy will not be effective for all severe/critical patients due to many reasons, but can be used in certain patients (e.g.: lower lymphocyte counts on admission) [96]. Low dosage of intravenous methylprednisolone (20-80mg for 3-5 days) was effective in some severe patients at early stage to reduce lung inflammation and increase radiological improvement [97]. Ciclesonide, an inhaled corticosteroid, can suppress coronavirus replication in cultured cells and might be a candidate drug for treatment [98]. Mo, P. observed that refractory patients were more likely to receive steroids as a treatment [99].

Discussion and Conclusion

SARS, MERS and COVID-19 have almost similar pathology and clinical features mainly affecting the lower respiratory tract. Steroids can be beneficial in these viral infections by suppressing SARS-CoV induced antibodies, T cells, B cells, cytokines, chemokines, complement signaling, antibody-dependent enhancement, vascular and hematological manifestations and inhibit viral replication via COX-2/PGE2 pathways. Steroids can also protects against cell apoptosis and enhance tissue recovery. Corticosteroids have shown some favorable outcomes in patients with SARS and COVID-19. Short course of prednisolone 1 mg per kilogram of body weight per day or initial use of pulse methylprednisolone therapy (methylprednisolone $\geqslant$ 500 mg/day) can be beneficial according to available literature. Combination of ribavirin, immunoglobulin, quinolone plus azithromycin with steroids can also be beneficial. However higher subsequent plasma viral load due to delayed virus clearance with early hydrocortisone treatment and aspergillosis after prolonged use of steroids have also been reported. In fact this lack of benefits of CSs in viral illness management have been explained due to over dose of CSs, used a water retention CSs at the inappropriate stage of illness and usage of drug beyond the therapeutic window limit [103,104]. Moreover it was also found that reduced time to recovery following early COVID-19 stage when inhaled corticosteroids (budesonide) was administrated early to COVID-19 infected patients [105]. Thus in these back ground, it can be suggested that steroids should be preferably given in early course of the disease before viremia comes into the diseases pathology (e.g. in the first week), short cause of the drug without prolog suppression of immune cells during viremia with antiviral drugs and immunoglobulin and moderate or high doses according to existing guideline in latter phase of illness. After reviewing the studies, it can be suggested that administration of steroids during a therapeutic window and in different phases of illness can have beneficial effects. Proper steroid plan in very early stage can prevent higher plasma viral load and help to prevent delayed virus clearance and secondary infections. Since most of the data are from observational studies, good-quality randomized trials using basic theory of pharmacology, immunology and virology is needed to

formulate a clear recommendation regarding steroid type (methyl prednisolone, prednisolone, hydrocortisone), dose, duration, route and timing. Even though there appeared to be some evidence that corticosteroids may be beneficial according to immunopathology and steroids pharmacological actions, up to now there are no a proper study done considering their action in early phase of illness when there is no high viral lord to clear recommendations on steroid use in COVID-19. Thus it can be concluded that CSs will be suggested to be used not only late phase of COVID -19 but also in early phase in selected patients If a proper clinical study is conducted with favorable outcome results.

Declarations

Ethical Approval

Not required.

Availability of Data and Material

The data set for this publication is available upon request from the authors.

Competing Interests

None to declare.

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None.

Authors' Contribution

SMRB Formulated the hypotheses on following topics such Corticosteroid actions on viral(SARS co V-2 SARS co V, dengue) immune pathology effectiveness of corticosteroid in COVID-19 treatment and management of COVID-19 and post viral Syndrome forCOVID-19, devised the project and review articles, the main conceptual ideas and proof outline wrote the manuscript. MNW and KGCYBW extracted and reviewed the literature of SARS CoV-2 infections and immunology and pharmacology of corticosteroids. SMTNS extracted the literature of SARS CoV-2 infections, immunology and helped to draw figures, HMMTBH corrected, edited the manuscript and supervised the review. All authors read and approved the final manuscript.

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Bibliography

1. Wang C., *et al*. "A novel coronavirus outbreak of global health concern". *Lancet* 395.10223 (2020): 470-473.

2. Shi H., *et al*. "Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study". *Lancet Infection Disease* (2020).

3. Chang D., *et al*. "Epidemiologic and Clinical Characteristics of Novel Coronavirus Infections Involving 13 Patients Outside Wuhan, China". *JAMA. American Medical Association* 323.11 (2020): 1092-1093.

4. Drosten C., *et al*. "Identification of a novel coronavirus in patients with severe acute respiratory syndrome". *New England Journal of Medicine* 348.20 (2003): 1967-1976.

5. Zaki AM., *et al*. "Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia". *New England Journal of Medicine* 367.19 (2012): 1814-1820.

6. Cheng VCC., *et al*. "Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection". *Clinical Microbiology Review* 20.4 (2007): 660-694.

7. Chan JF-W., *et al*. "Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan". *Emerging Microbes and Infections* 9.1 (2020): 221-236.

8. de Groot RJ., *et al*. "Middle East respiratory syndrome coronavirus (MERS-CoV): announcement of the Coronavirus Study Group". *Journal of Virology. American Society for Microbiology Journals* 87.14 (2013): 7790-7792.

9. Magazine R., *et al*. "Prescribing Patterns of Drugs in Acute Respiratory Distress Syndrome (ARDS): An Observational Study". *Journal of Clinical and Diagnostic Research* 9.2 (2015): FC01-04.

10. Wang H., *et al*. "Fatal aspergillosis in a patient with SARS who was treated with corticosteroids". *New England Journal of Medicine* 349.5 (2003): 507-508.

11. Stockman LJ., *et al*. "SARS: systematic review of treatment effects". Low D, editor. *PLoS Medicine* Public Library of Science 3.9 (2006): e343.

12. Marik PE., *et al*. "Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine". *Critical Care Medicine* (2008): 1937-1949.

13. Lansbury LE., *et al*. "Corticosteroids as Adjunctive Therapy in the Treatment of Influenza: An Updated Cochrane Systematic Review and Meta-analysis". *Critical Care Medicine* 48.2 (2020): e98-e106.

14. Delaney JW., *et al*. "The influence of corticosteroid treatment on the outcome of influenza A (H1N1pdm09)-related critical illness". *Critical Care BioMed Central* 20.1 (2016): 75-11.

15. Russell CD., *et al*. "Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury". *Lancet* 395.10223 (2020): 473-475.

16. Bandara SMR and Herath HMMTB. "Effectiveness of corticosteroid in the treatment of dengue - A systemic review". *Heliyon.* Elsevier 4.9 (2018): e00816.

17. Jin Y., *et al*. "Virology, Epidemiology, Pathogenesis, and Control of COVID-19". *Viruses.* Multidisciplinary Digital Publishing Institute 12.4 (2020): 372.

18. Gu J and Korteweg C. "Pathology and pathogenesis of severe acute respiratory syndrome". *American Journal of Pathology* 170.4 (2017): 1136-1147.

19. Li W., *et al*. "Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus". *Nature.* Nature Publishing Group 426.6965 (2003): 450-454.

20. Sims AC., *et al*. "Severe acute respiratory syndrome coronavirus infection of human ciliated airway epithelia: role of ciliated cells in viral spread in the conducting airways of the lungs". *Journal of Virology. American Society for Microbiology Journals* 79.24 (2005): 15511-15524.

21. Hamming I., *et al*. "Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis". *Journal of Pathology* John Wiley and Sons, Ltd 203.2 (2004): 631-637.

22. Yoshikawa T., *et al*. "Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells". *Journal of Virology* 83.7 (2009): 3039-3048.

23. Jeffers SA., *et al*. "CD209L (L-SIGN) is a receptor for severe acute respiratory syndrome coronavirus". *Proceedings of the National Academy of Sciences of the United States of America.* National Academy of Sciences 101.44 (2004): 15748-15753.

24. Marzi A., *et al*. "DC-SIGN and DC-SIGNR interact with the glycoprotein of Marburg virus and the S protein of severe acute respiratory syndrome coronavirus". *Journal of Virology. American Society for Microbiology Journals* 78.21 (2004): 12090-12095.

25. Boonnak K., *et al*. "Role of Dendritic Cells in Antibody-Dependent Enhancement of Dengue Virus Infection". *Journal of Virology. American Society for Microbiology Journals* 82.8 (2008): 3939-3951.

26. Pokidysheva E., *et al*. "Cryo-EM Reconstruction of Dengue Virus in Complex with the Carbohydrate Recognition Domain of DC-SIGN". *Cell.* Cell Press 124.3 (2006): 485-493.

27. Kuba K., *et al*. "A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury". *Nature Medicine.* Nature Publishing Group 11.8 (2005): 875-879.

28. Yumiko Imai., *et al*. "Angiotensin-converting enzyme 2 protects from severe acute lung failure". *Nature* 436.7047 (2005): 112-116.

29. Ying Meng., *et al*. "The Angiotensin-Converting Enzyme 2/Angiotensin (1-7)/Mas Axis Protects Against Lung Fibroblast Migration and Lung Fibrosis by Inhibiting the NOX4-Derived ROSMediated RhoA/Rho Kinase Pathway". *Antioxidants and Redox Signaling* 22.3 (2015): 241-258.

30. Ding Y., *et al*. "The clinical pathology of severe acute respiratory syndrome (SARS): a report from China". *Journal of Pathology* John Wiley and Sons, Ltd 200.3 (2003): 282-289.

31. Chan WS., *et al*. "Coronaviral hypothetical and structural proteins were found in the intestinal surface enterocytes and pneumocytes of severe acute respiratory syndrome (SARS)". *Modern Pathology* Nature Publishing Group 18.11 (2005): 1432-1439.

32. Zhang L., *et al*. "Antibody responses against SARS coronavirus are correlated with disease outcome of infected individuals". *Journal of Medical Virology* John Wiley and Sons, Ltd 78.1 (2006): 1-8.

33. Liu L., *et al*. "Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection". *JCI Insight. American Society for Clinical Investigation* 4.4 (2019): S6.

34. Lin YS., *et al*. "Antibody to severe acute respiratory syndrome (SARS)-associated coronavirus spike protein domain 2 cross-reacts with lung epithelial cells and causes cytotoxicity". *Clinical and Experimental Immunology* John Wiley and Sons, Ltd 141.3 (2005): 500-508.

35. Yang YH., *et al*. "Autoantibodies against human epithelial cells and endothelial cells after severe acute respiratory syndrome (SARS)-associated coronavirus infection". *Journal of Medical Virology*. John Wiley and Sons, Ltd 77.1 (2005): 1-7.

36. Wong CK., *et al*. "Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome". *Clinical and Experimental Immunology*. John Wiley and Sons, Ltd 136.1 (2004): 95-103.

37. Mahallawi WH., *et al*. "MERS-CoV infection in humans is associated with a pro-inflammatory Th1 and Th17 cytokine profile". *Cytokine.* Academic Press 104 (2018): 8-13.

38. Chaolin Huang., *et al*. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China". *The Lancet* Elsevier 395.10223 (2020): 497-506.

39. Liberman AC., *et al*. "Glucocorticoids in the regulation of transcription factors that control cytokine synthesis". *Cytokine and Growth Factor Reviews* 18 (2020): 45-56.

40. Liberman AC., *et al*. "Regulatory and Mechanistic Actions of Glucocorticoids on T and Inflammatory Cells". *Frontiers in Endocrinology (Lausanne). Frontiers* 9 (2018): 235.

41. Wandinger KP., *et al*. "Effect of high-dose methylprednisolone administration on immune functions in multiple sclerosis patients". *Acta Neurologica Scandinavica*. John Wiley and Sons, Ltd 97.6 (1998): 359-365.

42. Crockard AD., *et al*. "Transient immunomodulation by intravenous methylprednisolone treatment of multiple sclerosis". *Multiple Sclerosis* 1.1 (1995): 20-24.

43. Hodge Flower Han. "Methyl-Prednisolone Up-Regulates Monocyte Interleukin-10 Production in Stimulated Whole Blood". *Scandinavian Journal of Immunology.* Wiley/Blackwell (10.1111) 49.5 (1999): 548-553.

44. Moore KW., *et al*. "Interleukin-10 and the Interleukin-10 Receptor". *Annual Reviews* 4139 El Camino Way, P.O. Box 10139, Palo Alto, CA 94303-0139, USA 19.1 (2003): 683-765.

45. Hart KA., *et al*. "Effects of Low-Dose Hydrocortisone Therapy on Immune Function in Neonatal Horses". *Pediatric Research*. Nature Publishing Group 70.1 (2011): 72-77.

46. Bandara SMR and Herath HMMTB. "Corticosteroid actions on dengue immune pathology A review article". *Clinical Epidemiology and Global Health*. Elsevier (2019).

47. Barnes PJ. "How corticosteroids control inflammation: Quintiles Prize Lecture 2005". *British Journal of Pharmacology*. John Wiley and Sons, Ltd 148.3 (2016): 245-254.

48. Silwal P., *et al*. "Dexamethasone Induces FcγRIIb Expression in RBL-2H3 Cells". *Korean Journal of Physiology and Pharmacology* 16.6 (2012): 393-398.

49. Guilliams M., *et al*. "The function of Fcγ receptors in dendritic cells and macrophages". *Nature Reviews Immunology*. Nature Publishing Group 14.2 (2014): 94-108.

50. Nielsen DG. "The relationship of interacting immunological components in dengue pathogenesis". *Virology Journal.* BioMed Central 6.1 (2009): 211.

51. Peng Q., *et al*. "The role of anaphylatoxins C3a and C5a in regulating innate and adaptive immune responses". *Inflammation Allergy and Drug Targets* 8.3 (2009): 236-246.

52. Gorski JP., *et al*. "C4a: the third anaphylatoxin of the human complement system". *Proceedings of the National Academy of Sciences of the United States of America* 76.10 (1979): 5299-302.

53. Stoermer KA and Morrison TE. "Complement and viral pathogenesis". *Virology* 411.2 (2011): 362-373.

54. Gralinski LE., *et al*. "Complement Activation Contributes to Severe Acute Respiratory Syndrome Coronavirus Pathogenesis". Subbarao K, editor. *mBio* 9.5 (2018): 1666.

55. Weiler JM and Packard BD. "Methylprednisolone inhibits the alternative and amplification pathways of complement. Infection and Immunity". *American Society for Microbiology Journals* 38.1 (1982): 122-126.

56. Hammerschmidt DE., *et al*. "Corticosteroids inhibit complement-induced granulocyte aggregation. A possible mechanism for their efficacy in shock states". *Journal of Clinical Investigation. American Society for Clinical Investigation* 63.4 (1979): 798-803.

57. Tseng C-TK., *et al*. "Severe acute respiratory syndrome and the innate immune responses: modulation of effector cell function without productive infection". *Journal of Immunology. American Association of Immunologists* 174.12 (2005): 7977-7985.

58. Jaume M., *et al*. "Anti-severe acute respiratory syndrome coronavirus spike antibodies trigger infection of human immune cells via a pH- and cysteine protease-independent FcγR pathway". *Journal of Virology. American Society for Microbiology Journals* 85.20 (2011): 10582-10597.

59. Wan Y., *et al*. "Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry". *Journal of Virology* 94.5 (2020).

60. Delelis O., *et al*. "Integrase and integration: biochemical activities of HIV-1 integrase". *Retrovirology* 5.1 (2008): 114.

61. Moser M., *et al*. "Glucocorticoids down-regulate dendritic cell function in vitro and in vivo". *European Journal of Immunology*. John Wiley and Sons, Ltd 25.10 (1995): 2818-2824.

62. Ding Y., *et al*. "Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways". *Journal of Pathology.* John Wiley and Sons, Ltd 203.2 (2004): 622-630.

63. Hwang DM., *et al*. "Pulmonary pathology of severe acute respiratory syndrome in Toronto". *Modern Pathology*. Nature Publishing Group 18.1 (2005): 1-10.

64. Lee Y-R., *et al*. "MCP-1, a highly expressed chemokine in dengue haemorrhagic fever/dengue shock syndrome patients, may cause permeability change, possibly through reduced tight junctions of vascular endothelium cells". *Journal of Genetic Virology* 87 (2006): 3623-3630.

65. Raaben M., *et al*. "Cyclooxygenase activity is important for efficient replication of mouse hepatitis virus at an early stage of infection". *Virology Journal. BioMed Central* 4.1 (2007): 55-65.

66. Steer SA and Corbett JA. "The Role and Regulation of COX-2 during Viral Infection". 16.4 (2004): 447-460.

67. Sander WJ, ., *et al*. "Prostaglandin E2 As a Modulator of Viral Infections". *Frontiers in Physiology* 8 (2017): 89.

68. Lin C-K., *et al*. "Cyclooxygenase-2 facilitates dengue virus replication and serves as a potential target for developing antiviral agents". *Scientific Reports*. Nature Publishing Group 7.1 (2017): 299.

69. Lee C-H., *et al*. "Altered p38 mitogen-activated protein kinase expression in different leukocytes with increment of immunosuppressive mediators in patients with severe acute respiratory syndrome". *Journal of Immunology* 172.12 (2004): 7841-7847.

70. Liu M., *et al*. "Amino acids 1 to 422 of the spike protein of SARS associated coronavirus are required for induction of cyclooxygenase-2". *Virus Genes* 33.3 (2006): 309-317.

71. Santini G., *et al*. "The human pharmacology of monocyte cyclooxygenase 2 inhibition by cortisol and synthetic glucocorticoids". *Clinical Pharmacology and Therapeutics*. John Wiley and Sons, Ltd 70.5 (2001): 475-483.

72. Lee N., *et al*. "Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients". *Journal of Clinical Virology* 31.4 (2004): 304-309.

73. Menou A., *et al*. "Human airway trypsin-like protease exerts potent, antifibrotic action in pulmonary fibrosis". *FASEB Journal* 32.3 (2018): 1250-1264.

74. Yang Y., *et al*. "Bcl-xL inhibits T-cell apoptosis induced by expression of SARS coronavirus E protein in the absence of growth factors". *Biochemical Journal* 392 (2005): 135-143.

75. Tan Y-J., *et al*. "Overexpression of 7a, a protein specifically encoded by the severe acute respiratory syndrome coronavirus, induces apoptosis via a caspase-dependent pathway". *Journal of Virology. American Society for Microbiology Journal* 78.24 (2004): 14043-14047.

76. Xu J., *et al*. "Orchitis: a complication of severe acute respiratory syndrome (SARS)". *Biological Reproduction* 74.2 (2006): 410-416.

77. Chau T-N., *et al*. "SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases". *Hepatology* 39.2 (2004): 302-310.

78. Hagimoto N., *et al*. "TGF-beta 1 as an enhancer of Fas-mediated apoptosis of lung epithelial cells". *Journal of Immunology. American Association of Immunologists* 168.12 (2002): 6470-6478.

79. Meßmer UK., *et al*. "Suppression of apoptosis by glucocorticoids in glomerular endothelial cells: effects on proapoptotic pathways". *British Journal of Pharmacology*. Wiley/Blackwell (10.1111) 129.8 (2000): 1673-1683.

80. Radomski MW., *et al*. "Glucocorticoids inhibit the expression of an inducible, but not the constitutive, nitric oxide synthase in vascular endothelial cells". *Proceedings of the National Academy of Sciences of the United States of America* 87.24 (1990): 10043-10047.

81. Quiros M., *et al*. "Macrophage-derived IL-10 mediates mucosal repair by epithelial WISP-1 signaling". *Journal of Clinical Investigation. American Society for Clinical Investigation* 127.9 (2017): 3510-3520.

82. Tabardel Y., *et al*. "Corticosteroids increase blood interleukin-10 levels during cardiopulmonary bypass in men". *Surgery* 119.1 (1996): 76-80.

83. Meduri GU., *et al*. "Effect of prolonged methylprednisolone therapy in unresolving acute respiratory distress syndrome: a randomized controlled trial". *JAMA* 280.2 (1998): 159-165.

84. Bernard GR., *et al*. "High-Dose Corticosteroids in Patients with the Adult Respiratory Distress Syndrome". *Massachusetts Medical Society* 317.25 (2010): 1565-1570.

85. Singh A., *et al*. "Role of Corticosteroids Use in Ards: Comparison of Systematic Review and Meta-Analysis". *Value Health* 17.7 (2014): A726.

86. Horita N., *et al*. "Impact of Corticosteroids on Mortality in Patients with Acute Respiratory Distress Syndrome: A Systematic Review and Meta-analysis". *Intern Medicine. The Japanese Society of Internal Medicine* 54.12 (2005): 1473-1479.

87. Lee N., *et al*. "A Major Outbreak of Severe Acute Respiratory Syndrome in Hong Kong". *New England Journal of Medicine* 348.20 (2003): 1986-1994.

88. Ho JC., *et al*. "High-dose pulse versus nonpulse corticosteroid regimens in severe acute respiratory syndrome*". American Journal of Respiratory and Critical Care Medicine* 168.12 (2003): 1449-1456.

89. Lew TWK., *et al*. "Acute Respiratory Distress Syndrome in Critically Ill Patients With Severe Acute Respiratory Syndrome". *JAMA. American Medical Association* 290.3 (2003): 374-380.

90. Zhao Z. "Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China". *Journal of Medical Microbiology. Microbiology Society* 52.8 (2003): 715-720.

91. Fowler RA. "Critically Ill Patients With Severe Acute Respiratory Syndrome". *JAMA. American Medical Association* 290.3 (2003): 367.

92. Booth CM., *et al*. "Clinical Features and Short-term Outcomes of 144 Patients With SARS in the Greater Toronto Area". *JAMA. American Medical Association* 289.21 (2003): 2801-2809.

93. Arabi YM., *et al*. "Corticosteroid Therapy for Critically Ill Patients with Middle East Respiratory Syndrome. American Journal of Respiratory and Critical Care Medicine". *American Thoracic Society* 197.6 (2018): 757-767.

94. Wang Y., *et al*. "Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China". *medRxiv. Cold Spring Harbor Laboratory Press* (2020).

95. Zhou Z-G., *et al*. "Short-Term Moderate-Dose Corticosteroid Plus Immunoglobulin Effectively Reverses COVID-19 Patients Who Have Failed Low-Dose Therapy". *Preprints* (2020).

96. Shang J., *et al*. "The Treatment and Outcomes of Patients with COVID-19 in Hubei, China: A Multi-Centered, Retrospective, Observational Study". *SSRN Journal* (2020).

97. Qi D., *et al*. "Epidemiological and clinical features of 2019-nCoV acute respiratory disease cases in Chongqing municipality, China: a retrospective, descriptive, multiple-center". *medRxiv* (2020).

98. Matsuyama S., *et al*. "The inhaled corticosteroid ciclesonide blocks coronavirus RNA replication by targeting viral NSP15". *bioRxiv. Cold Spring Harbor Laboratory* (2020).

99. Mo P., *et al*. "Clinical characteristics of refractory COVID-19 pneumonia in Wuhan, China". *Clinical Infection Disease* (2020).

100. Jingwei Biana and Zijian Li. "Angiotensin-converting enzyme 2 (ACE2): SARS-CoV-2 receptor and RAS modulator". *Acta Pharmaceutica Sinica B* 13 (2020).

101. Holappa M., *et al*. "Many faces of renin-angiotensin system-focus on eye". *Open Ophthalmology Journal* 11 (2017): 122.

102. Cynthia Magro., *et al*. "Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases". *Translational Research* 220 (2020): 1-13.

103. Bandara SMR and Herath HMMTB. "Effectiveness of corticosteroid in the treatment of dengue - A systemic review". *Heliyon.* Elsevier 4.9 (2018): e00816.

104. SM Rathnasiri Bandara., *et al*. "COVID-19 Treatment and Post-COVID-19 Complication Syndrome: A Review". *Acta Scientific Microbiology* 3.5 (2020).

105. Sanjay Ramakrishnan., et al. " Inhaled budesonide in the treatment of early COVID-19 illness: a randomised controlled trial".

106. Zhen Xiang., *et al*. "Glucocorticoids improve severe or critical COVID-19 by activating ACE2 and reducing IL-6 levels". *International Journal of Biological Sciences* 16.13 (2020): 2382-2391.

107. Walters RW., *et al*. "Adenovirus fiber disrupts CAR-mediated intercellular adhesion allowing virus escape". *Cell* 110.6 (2002): 789-99.

108. Flavio De Maioab., *et al*. "Improved binding of SARS-CoV-2 Envelope protein to tight junction-associated PALS1 could play a key role in COVID-19 pathogenesis". *Microbes and Infection* 22.10 (2020): 592-597.

109. Yuksel H., *et al*. "Vascular endothelial growth factor antagonism restores epithelial barrier dysfunction via affecting zonula occludens proteins". *Experimental and Therapeutic Medicine Spandidos Publications* 10.1 (2015): 362-368.