

Treatment with Corticosteroids may Link to Higher Risk of COVID-19 Disease?

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ABSTRACT

Corticosteroids are one of the important natural hormones released in the body that play a vital role in metabolism due to their intense anti-inflammatory, immunomodulatory and immune suppressive activity. These are most prescribed medications available in various dosage forms like topical formulations, inhalers and injectables. The current outbreak of corona virus disease COVID-19 became a global threat and primary concern worldwide. In respiratory patients, the use of non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids exacerbate the disease symptoms of COVID-19 patients, as they are often regarded as immunosuppressive drugs. Inhaled corticosteroids (ICS) are considered as first line treatment of asthma and chronic obstructive pulmonary disease (COPD). COVID-19 disease led the upper respiratory tract illness. ICS are used in the treatment of early symptoms of COVID-19 disease in low doses. Asthmatic patients or patients with chronic obstructive lung disease, who are on regular use of ICS were found to have a low risk of early symptoms of severely ill COVID-19 disease. Although there appeared to be some evidence that corticosteroid therapy may be beneficial in treatment of corona virus disease, but it is also reported to be applicable only at the early acute phase. The literature records revealed that injectable formulations of corticosteroids are known to suppress the immunity in patients infected with SARS-CoV2. The present review is to study the different formulations of corticosteroids and their possible use in COVID-19 progression.

Key words: Corticosteroids; COVID-19 disease; Risk factors; ADRS; Cytokine storm.

1. INTRODUCTION

Corticosteroids are a class of hormones released from adrenal cortex as glucocorticoids and mineralocorticoids. Glucocorticoids plays an important role in metabolism of calcium, proteins, and carbohydrates and due to their intense anti-inflammatory, immunomodulatory, and immunosuppressive activity, they are used in the treatment of many conditions such as malignant, allergic conditions, ophthalmic and neurological diseases. Since from December 2019, the outbreak of novel serious acute respiratory syndrome corona virus (SARS-CoV2) was labeled as a global pandemic by World Health Organization.¹ Patients who are currently on corticosteroid therapy are at higher risk for developing corona virus infection because of having a weak immunity as steroids weakens the immune system and the patients taking corticosteroids on daily basis in

conditions such as asthma, allergy, arthritis are at higher risk for infection by COVID-19.^{2,3} The COVID-19 disease occurs in different stages, including upper and lower respiratory tract infections in mild stage, which may progress to pneumonia in later stage.⁴

1.1. Importance of Corticosteroids

The steroids constitute a group of structurally related compounds that are widely distributed in plants, animals and fungi, the basic nucleus of steroids consist of cyclopentane phenanthrene ring structure, by modifications in their structures at specific positions that are available for suitable substitution new derivative of steroidal drugs can be developed.⁵ Steroidal drugs and related products are widely used therapeutic agents in the treatment of many inflammatory conditions, cancer treatment, hormone replacement therapy, birth control and dermatological disorders.⁶ Medicinal chemistry play an important

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role in drug discovery and development by studying and identifying new chemical derivatives, compounds, molecules, further by linking many scientific disciplines.⁷

1.2. Pathogenesis of Adverse Drug Reactions (ADRS) in COVID-19

In serious state of COVID-19 (SARS-CoV2) disease, there is progression after a mid-incubation period of about four days (interquartile range of 2-7 days), in which the cytokine storm is associated with the development and progression of adult respiratory distress syndrome.^{8,9} As Adverse Drug Reactions (ADRS) starts developing from the second week onwards, an explosive immune response from the host causes uncontrolled viral replication. The pathological epithelial cells may increase and induce the release of cytokine or ‘cytokine storm’ along with increased inflammation and immune suppression because of uncontrolled viral replication, which is identified by reduced memory CD4+T helper cells with increased CD8 cytotoxic response.¹⁰

Antivirus immune response in the first phase leads the way to eradicate the virus by the immune mediated pulmonary injury, which initiates at the epithelial-interstitial-endothelial cells, with release of inflammatory neutrophils and macrophages as shown in Figure 1, this leads to reduction in alveolar surfactant resulting in gaseous deficiency and impedes alveolar patency.^{11,12}

In second phase, there is hyper inflammatory state due to the unrestrained viral replication, which induces angiotensin-converting enzyme 2 (ACE2) which further hyperactivates the immune system, worsening the inflammatory state. Due to dysfunctional lymphocytes, patients in this stage reveals lymphopenia with a reduction in B cells, CD4, CD8 T cells and CD16⁺ (NK) natural killer cells.^{13,14} The cytokine release will initiate vascular inflammation, progression of coagulation and hypotensive shock which results in multi-organ failure that can lead to death. Some studies shows that any intervention that will prevent this pathological condition will also prevent lungs damage and pulmonary

thromboembolism. With these pathophysiological interventions, corticosteroids have been recommended in COVID-19.

Since corticosteroids are considered as immunosuppressive as they impair innate immunity system of body, their utilization in COVID-19 is largely discouraged as this may worsen the viral propagation.¹⁵ Patients who are taking steroids maintenance dose are on low risk to develop severe pneumonia in the presence of COVID-19 disease. The earlier studies on serious acute respiratory syndrome coronavirus (SARS-COV-1) and Middle East respiratory syndrome coronavirus (MERS-COV) had showed undesirable effects with corticosteroids treatment.^{16,17}

Recently two commentaries published in Lancet also recorded that the use of corticosteroids should be restricted in the treatment of COVID-19 disease.^{18,19} World Health Organization (WHO) and the Center for Disease Control and Prevention (CDC), also advised especially against the utilization of corticosteroids for the immune modulation purpose.^{20,21} Varied reports states that injectable formulations of corticosteroids are known to suppress the immunity in patients infected with SARS-CoV2. ICS are considered as first line treatment of asthma and chronic obstructive pulmonary disease (COPD), for COVID-19 their use should be in low doses, Asthmatic patients or those with chronic obstructive lung disease, who are on regular use of ICS were found to have lesser risk of early symptoms of severely ill pandemic but their use is still controversial.²²

2. METHODOLOGY

A systematic electronic search was carried out using the following electronic databases: Scopus, PubMed, Nature and Springer, the inclusion standards were to retrieve the original articles and presented in the text to assess the treatment with corticosteroids during the COVID-19 outbreak up to October 2020. Research terms used for inclusion are “COVID-19” or “SARS-CoV2”, “ADRS”, “Cytokine storm” and “Corticosteroids”.

3. USE OF CORTICOSTEROIDS IN DIFFERENT TREATMENTS BY DIFFERENT ROUTES

Corticosteroids can be administered orally, topically, injected locally, and can be inhaled.²³ As corticosteroids are most prescribed medications, topical formulations are commonly prescribed in dermatological conditions and available in variety of potencies and preparations.²⁴ Topical corticosteroids market segmentation includes various preparations (Table 1). In elder population, the use of topical corticosteroids during COVID-19 outbreak

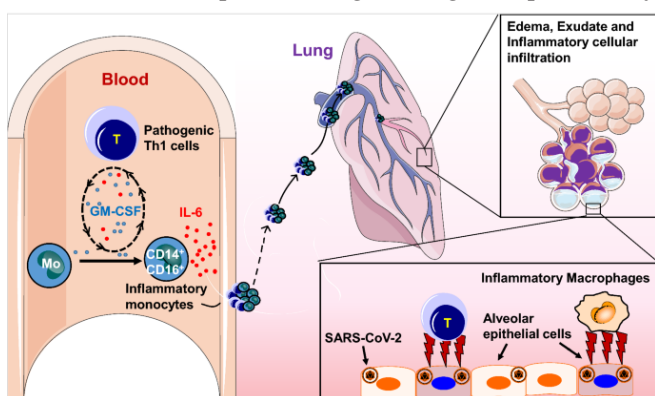


Figure 1: Pathogenesis of ADRS in COVID -19¹²

for seborrheic dermatitis and other skin manifestations are recommended. In skin problems like psoriasis and superficial fungal infections, mild to moderate potency of corticosteroid are recommended.²⁵ The injectable corticosteroids are known to reduce the immunity and suppress the hypothalamic pituitary axis. A research study was carried out in China in which it was observed in patients infected with SARS-CoV2, the use of steroids has further worsened the symptoms of the SARS-CoV2 disease. The study recommended avoiding the injectable form of corticosteroids in patients infected with the SARS-CoV2. The study also recommended other guidelines and interventions to be considered. The commonly used injectable formulations are shown in Table 1.²⁶

3.1. Inhaled Corticosteroids

ICS are the cornerstone for the treatment of asthma and chronic obstructive pulmonary disease (COPD), these are developed recently as pressurized metered dose inhaler and dry powdered inhaler devices.^{36,37} As COVID-19 causes the upper respiratory tract illness, ICS are used in the treatment of early symptoms of covid-19 disease. Asthmatic patients or those with chronic obstructive lung disease on regular use of ICS were found to have a low risk of early symptoms of severely ill pandemic.³⁸ During the COVID-19 pandemic, many physicians were

concerned about the use of ICS for individuals positive for SARs-COV-2, should they continued ICS or should stop them, due to their immunosuppressive potential. For asthma and COPD patients, ICS arises many questions such as either they increased or decreased the risk for COVID-19 or the use of ICS modify the risk for COVID-19.³⁹

3.1.1. Different Types of Inhalers

Dry powder inhalers (DPIs) are novel, widely used and become a known drug delivery platform as they are being used in the treatment of obstructive pulmonary disease and asthma, over 20 devices are present in the market of DPIs, and these are preferred over nebulizers and pressurized metered dose inhalers and are ideal as compare to other inhalers.⁴⁰ The types of dry powder inhalers with their doses and drugs available are mentioned in Table 2.⁴¹

3.2. Injectable Forms of Corticosteroids

The injectable corticosteroids are used in many conditions of chronic pain as their primary role is in the management of pain and reduction of inflammation through direct delivery of drug to the site of action.⁴² There are many injectable forms of corticosteroids available with different routes of administration and indications to maximize

Table 1: Available dosage forms of corticosteroids with potencies and applications

	Super Potent (%)	Highly Potent (%)	Moderately Potent (%)	Mildly Potent (%)
<i>Topical Corticosteroids</i>	Clobetasol Propionate Ointment (0.05) Betamethasone Dipropionate (0.05)	Mometasone Ointment (0.1)	Mometasone furoate cream (0.1)	Clobetasone butyrate (0.05)
		Betamethasone Dipropionate Cream (0.5)	Fluticasone propionate ointment/cream (0.05)	Aclometasone Dipropionate (0.05)
		Beclomethasone Dipropionate (0.025)	Betamethasone Valerate (0.05)	Hydrocortisone acetate (0.1)
		Prednicarbate ointment (0.25)	Desonide cream (0.05)	
<i>Applications</i>	Used in the treatment of contact eczema, Atopic dermatitis, Lichen planus, Vitiligo, Psoriasis (specific forms), Phimosis, Lichen sclerosis, severe cutaneous diseases.			
<i>References</i>	27,28,29,30			
<i>Injectable Corticosteroids</i>	<i>Long Acting</i>	<i>Intermediate Acting</i>	<i>Short Acting</i>	<i>References</i>
	Dexamethasone Triamcinolone Betamethasone	Methyl Prednisolone Prednisolone Prednisone	Hydrocortisone Cortisone	31,32,33
	<i>Applications</i>	Used in the treatment of Acute generalized eczema, Anaphylactic reactions, Connective tissue disease, Vasculitis, Severe lichen planus, COPD, Acute spinal cord injury, Tuberculosis pleurisy, Bacterial Meningitis, Inflammatory conditions.		
			<i>Applications</i>	<i>References</i>
<i>Inhaled Corticosteroids</i>	Beclomethasone Fluticasone Budesonide Fluticasone Propionate Ciclesonide		Used in the treatment of upper respiratory tract conditions Asthma, chronic obstructive pulmonary disease (COPD)	34,35

Table 2: Types of dry powder inhalers with dose and pharmaceutical forms of corticosteroids

S. No.	Device (Patent License)	Dose	Drugs Available	References
1	Rotahaler (GlaxoSmithKline)	1 Capsule Single Dose	Beclomethasone dipropionate, Salbutamol	46
2	Spinhaler (Aventis)	1 Capsule Single Dose	Sodium cromoglycate	47
3	Diskhaler (GlaxoSmithKline)	4,8 Blister Multi Dose	Salmeterol, Salbutamol	48
4	Turbuhaler (Astra Zeneca)	200 Bulk Reservoir Multi Dose	Formoterol, Budesonide Formoterol	49
5	Diskus (GlaxoSmithKline)	60 Blisters Multi Dose	Salbutamol, Salmeterol	48

Table 3: Systemic injectable pharmaceutical forms of corticosteroids

Route of Administration	Generic Name	Brand Name	Indication	References
Epidural steroid injection	Methyl prednisolone and betamethasone	Solumedrol Depomedrol Betnelan	Spinal stenosis, spondylolisthesis, Herniated disc, Degenerative disc, sciatica	50,51
Facet joint Injection	Betamethasone sodium phosphate	Celestone	Acute or chronic conditions of inflamed facet joints	51,52
IV/IM	Dexamethasone	Decadron Dexamax	Allergic conditions, asthma, inflammatory conditions	53

Table 4: Ophthalmic preparations of corticosteroids with clinical indications

Ophthalmic Dosage Forms	Generic Names	Brand Names	Clinical Indications	References
Ointments	Tobramycin 0.3% dexamethasone 0.1%, Sulphacetamide sodium prednisolone, Betamethasone	Dextatob eye ointment, Blephamide eye ointment, Betnesol eye ointment	Used in the treatment of macular oedema of retino vascular conditions, Scleritis and episcleritis, Uveal tract inflammation,	55
Drops	Dexamethasone sodium phosphate, Sulphacetamide sodium prednisolone, Betamethasone, Prednisolone acetate	Decadron eye drops, Blephamide eye drops, Betnesol eye drops, Predforte eye drops	sympathetic ophthalmitis, after injury or surgery, herpes zoster ophthalmicus, optic neuritis	56,57
Intravitreal Injection	Triamcinolone acetonide	Kenalog	Vein occlusions, inflammatory conditions, Macular edema secondary to diabetes	58

the benefits and reducing the side effects systemically (Table 3).⁴³ The indications for the injectable forms of corticosteroids are in the treatment of spine and radicular pain, musculoskeletal pain conditions, osteoarthritis, tendinitis, synovitis, rheumatoid arthritis and related conditions.⁴⁴ Recent use of corticosteroid in COVID-19 disease may worsen the condition more, as they suppress the immunity.⁴⁵

3.3. Local Application of Corticosteroids

A wide range of local ophthalmic corticosteroids preparations are available for topical use in the form of creams, ointments, gels and drops, used to treat inflammation, pain and in surgical conditions specifically made to be administered into or around the eye.⁵⁴ Topical drops and ointments are the primary methods

for the treatment of ophthalmic conditions; however, the ocular penetration of topical corticosteroids depends on the drug concentration, formulation or composition of corticosteroids and the vehicle composition.²⁴ The formulation descriptions of ophthalmic preparations of corticosteroids are shown in Table 4.

4. DISCUSSION

Present review summarizes the literature concerning the usage of corticosteroids during the recent global Covid-19 outbreak. Exacerbations of asthma and other chronic respiratory diseases are linked with increased airway inflammation that leads to increased respiratory symptoms.⁵⁹ Corticosteroids are broad immunosuppressive agents that decreases these features

to help clinical recovery, but the supervision from WHO instructs contrary to the use of corticosteroids, if the Covid-19 is susceptible.⁶⁰ Based on the earlier data, regardless of potentially beneficial anti-inflammatory effects, the corticosteroids either (inhaled or systemic) inhibits the production of life-threatening antiviral mediators type I and III interferons. Various *in vitro* and *in vivo* experiments of asthma-relevant viruses such as rhinovirus, influenza and respiratory syncytial virus (RSV) revealed all these distinct effects that precipitate augmentation in virus replication⁶¹ and increases the risks of developing virus-mediated mucus hypersecretion and secondary bacterial infections. Similar harmful effects are expected with the use of corticosteroids, if used in COVID-19 disease condition. Therefore, studies in patients with coronavirus infections (e.g., SARS-CoV-1, MERS-CoV) have shown that corticosteroids increase viraemia and interrupt viral clearance with no evidence of clinical benefit.⁶²

5. FUTURE CONCERN

Recent advances in the basic science of corticosteroids explain the clinical differences of these compounds related to safety and efficacy, by understanding, this can lead to the future discovery of additional novel corticosteroids.⁶³ In many mucocutaneous disorders, corticosteroid therapy is still the central focus; systemic therapy is limited to severe disorders while the topical therapy still considered as the first line treatment. Innovative drug delivery systems can prolong the retention time of drug on the mucosal membrane, which can exacerbate the symptoms of COVID-19 and thus avoid the side effects of conventional formulations.⁶⁴ Inhaled corticosteroids (ICS) are the cornerstone for the treatment of asthma and chronic obstructive pulmonary disease (COPD), As COVID-19 causes the upper respiratory tract illness, ICS are used in the treatment of early symptoms of covid-19 disease. Still ICS efficacies in COVID-19 are ongoing in various clinical settings, the results of which are eagerly awaited.⁶⁵

6. CONCLUSION

In conclusion, recent research shows a clue and hope for the use of ICS against COVID-19, although exact mechanism and large number of facts are still to be discovered. Although ICS are used in the treatment of early symptoms of covid-19 disease, but their therapeutic intervention still need to be studied and clinical trials assessing their efficacy in COVID-19 are continuing in diverse clinical settings, the results are still awaited.

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