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Ciclesonide Use in COVID-19: Not All Steroids Are the Same

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Abstract

Introduction: The inflammatory mechanisms of COVID-19 suggest that corticosteroids may be beneficial, but their benefits must outweigh their potential risks. The RECOVERY trial results suggest that dexamethasone 6 mg/day (but not other steroids) may confer mortality benefits on ventilated COVID-19 patients. **Methods:** This is a narrative review of the literature about the use of ciclesonide and dexamethasone for COVID-19 patients. Literature is being created rapidly and this review is offered as a state-of-the-science narration. **Results:** The SARS-CoV-2 virus is an RNA virus whose RNA is transcribed via open reading frames, making its elimination difficult. Coronaviruses have evolved multiple strategies for proteolytic activation of the spike; viral replication occurs entirely in the cytoplasm. In this connection, the RNA-cleaving endoribonuclease (NSP-15 also known as EndoU) may play a key role by facilitating viral double-stranded RNA recognition by the host's macrophages. Furthermore, the virus is able to undergo RNA recombination rapidly, enabling it to evade host immunity and develop drug resistance. Ciclesonide is an inhaled corticosteroid that reduces lung inflammation and blocks the activity of specific kinases which may explain its anti-inflammatory effect. Dexamethasone is known to reduce mortality in ventilated COVID-19 patients. **Discussion:** Systemic corticosteroids were used in previous coronavirus epidemics (SARS and MERS) and pulmonary histology of these patients is similar to those in COVID-19 patients. Acute respiratory distress syndrome is the main cause of death in most COVID-19 infections and steroids may be effective in addressing that condition, brought on by cytokine storm. However, it should be noted that inhaled steroids likely have a narrower window for effect than

systemic regimens. **Conclusion:** Dexamethasone has been proven to confer mortality benefits on ventilated COVID-19 patients and may be used with inhaled ciclesonide, which has few side effects and can be locally metabolized. Further study is needed.

1. What Is Known and Objective

The current pandemic due to the coronavirus disease 2019 (COVID-19) has spurred an effort to deploy the rational use or repurpose of approved registered pharmacological agents with potential efficacy. The inflammatory mechanisms of severe COVID-19 infection [1] [2] suggest that corticosteroids may be useful. However, there is evidence that argues against the routine systemic use of different types of corticosteroids, as the drug-associated side effects may often outweigh their potential benefits [3]. This is in line with previous recommendations from the World Health Organization (WHO) on the management of severe acute respiratory distress syndrome (ARDS) due to COVID-19, which advises against the use of steroids unless indicated for another reason [4]. Recent results from the UK-based RECOVERY trial emphasize the need to reevaluate this generalization, because it has been shown that dexamethasone treatment 6 mg/day significantly reduced 28-day mortality in patients with COVID-19 on ventilator support [5]. Notably, treatment arms with other steroids such as prednisolone, hydrocortisone, or methylprednisolone sodium succinate in the same study did not reduce mortality [5]. Nevertheless, there is much to be elucidated about the use of corticosteroids for COVID-19 patients in terms of specific agents, risks versus benefits, routes of administration, and mechanisms of action. Therefore, the purpose of this narrative review was to investigate the current knowledge with regard to mechanism and potential clinical rationale for further studies on inhaled versus oral steroids, especially with ciclesonide and dexamethasone.

2. Methods

A search in MEDLINE (English) using the terms "COVID-19", "inhalation steroids", "ciclesonide", and "dexamethasone" was conducted. Because the existing body of literature on the current pandemic is rapidly evolving, the authors also searched for relevant sources using Google Scholar, including preprints, until 16 July 2020 [6] [7]. The authors also implemented a broad dynamic approach and included information on aspects such as virology, molecular biology, immunology, genetics, biochemistry, pharmacology, pathophysiology, and clinical application to current date with special attention on ciclesonide and the latest clinical results using dexamethasone.

3. Results

3.1. About SARS-CoV-2

Like polio, measles, Ebola, and flu viruses, the currently pandemic virus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an RNA virus. Human strains of various coronaviruses are associated with approximately 15 percent of cases of the common cold [8]. In the 1970s and early 1980s, coronavirus virion proteins and nested-set arrangements of mRNAs were identified and the discontinuous nature of coronavirus transcription was initially demonstrated [9]. The first published sequence of a coronavirus gene appeared in 1983, starting an era of whole genome sequencing of four coronaviruses [10].

Coronaviruses have the largest RNA of all known RNA viruses. Its RNA is transcribed via open reading frames. This peculiarity increases the efficacy of viral replication and mutagenesis and makes it more difficult for the human immune system to eliminate [11]. The SARS-CoV-2 genome encodes 27 proteins needed by the virus to infect humans and to replicate [12]. These proteins include: the notorious spike protein, which recognizes angiotensin-converting enzyme 2 (ACE2) receptor in the initial stage of infection to gain intracellular access; two proteases, which cleave viral and human proteins; and the RNA polymerase (RdRp), which synthesizes viral RNA. The genome also contains a large replicase gene, encompassing nonstructural proteins (NSPs), followed by structural and accessory genes [13]. The S glycoprotein of coronaviruses, the main determinant of host cell attachment and viral entry, is not well conserved. Most human coronaviruses use different host cell receptors for viral entry and may also require different host cell proteases that allow fusion of viral and cellular membranes [14].

Coronaviruses have evolved multiple strategies for proteolytic activation of the spike, and a large number of host proteases have been shown to proteolytically process the spike protein. These include, but are not limited to, endosomal cathepsins, cell surface transmembrane protease/serine proteases, furin, and trypsin [15]. The most conserved proteins among coronaviruses are NSPs involved in essential functions of the viral lifecycle [16]. Coronavirus replication takes place entirely in the cytoplasm, and it is believed that nuclear functions are not required for RNA synthesis [17]. Thus, viral RNA transcription does not involve the conventional RNA splicing machinery present in the nucleus.

The structural proteins that make up the virion are less conserved than NSPs, and accessory proteins are only functionally conserved among very closely related viruses [18]. While several functions of NSPs have been linked to RNA replication and processing of RNA, the roles of other proteins are poorly understood or remain unknown [19]. The NSPs perform essential functions in immune antagonism through formation of the viral replication complex and double membrane vesicles, which shield the viral RNA, viral RNA proofreading, binding of nucleic acid, helicase activity, and so on [20]. Another essential element of the virus lifecycle is proteolytic processing of viral polyproteins into functional

NSPs by two viral proteases, 3CLpro and PLpro. Specifically, 3CLpro, also known as NSP5, is first automatically cleaved from polyproteins to produce mature enzymes, and then further cleaves downstream NSPs at 11 sites to release NSP14-NSP16. The 3CLpro directly mediates the maturation of NSPs, which is essential in the life cycle of the virus [21].

In addition to polymerase and protease functions, other essential functions performed by the NSPs of the coronavirus include immune antagonism, double membrane vesicle organization, scaffolding for replication complex formation, nucleic acid binding, helicase activity, and viral RNA proofreading, which may be future targets of coronavirus specific antiviral drug discovery [22].

3.2. NSP-15 and Its Role in Coronavirus Biology

Of particular interest in this context is one NSP in particular, the RNA-cleaving endoribonuclease (NSP15). The NSP15-associated endoribonuclease (EndoU) domain is one of the most conserved proteins among corona- and related viruses. NSP15 is also referred to as coronavirus EndoU in the scientific literature. However, the role of NSP15 in coronavirus replication was enigmatic, as EndoU-deficient coronaviruses were viable and replicated to near wild-type virus levels in fibroblast cells. Nevertheless, NSP15 is essential in coronavirus biology [23]-[28]. A breakthrough in the understanding of the role of EndoU was demonstrated in recent studies, which showed that EndoU mediates the evasion of viral double-stranded RNA (dsRNA) recognition by host sensors in macrophages [29]. There are also suggestions that NSP15 degrades viral RNA to hide it from the host defenses. The loss of NSP15 activity also resulted in greatly attenuated disease in mice and stimulated a protective immune response. Taken together, these findings demonstrate that coronavirus NSPs are critical for the evasion of host dsRNA sensors in macrophages [30].

3.3. SARS-Cov-2 Mutations

RNA viruses are characterized by a high mutation rate, up to a million times higher than that of their hosts, and SARS-CoV-2 is no exception [31]. It is also important to recognize whether the presence of some mutations might correlate with different SARS-CoV-2 mortality rates. Viral mutagenic capability depends upon several factors, including the fidelity of viral enzymes that replicate nucleic acids, such as SARS-CoV-2 RNA dependent RdRP [32]. Thus, recombination is a well-characterized feature of coronavirus biology. It can potentially provide a genetic mechanism by which coronaviruses maintain their sequence integrity. In light of the large size of the coronavirus RNA, it is predictable that most of the viral RNA molecules would contain one or more mutations, due to the high error frequencies of RNA polymerases; homologous recombination repair may provide a mechanism for the virus to stabilize their genome and increase fidelity across generations.

One unique genetic feature of coronaviruses is their ability to undergo RNA

recombination at a very high frequency [33]. Mutation rate drives viral evolution and genome variability, thereby enabling viruses to escape host immunity and to develop drug resistance [34] [35]. Based on genomic sampling over time, the substitution rate is estimated to be 0.00084 per site per year as of 16 May 2020, two- to six-fold lower than the substitution rate for influenza (0.004 - 0.005 subst/site/yr for influenza A and for influenza B [36]. Across its ≈ 30,000 base-pair genome, the SARS-CoV-2 thus undergoes roughly one genetic change every other week. To date, over 14,000 mutations have been identified [37].

These findings suggest that the SARS-Cov-2 virus is evolving, and that unique European, North American, and Asian strains might coexist, each with a different mutation pattern. A SARS-CoV-2 variant carrying the spike protein amino acid change D614G has become the most prevalent form in the global pandemic. Dynamic tracking of variant frequencies revealed a recurrent pattern of G614 increase at multiple geographic levels: national, regional, and municipal. The shift occurred even in local epidemics where the original D614 form was well established prior to the introduction of the G614 variant. The consistency of this pattern suggests that the G614 variant may have a fitness advantage [38].

Since RNA viruses need their RdRP for replication, this means that, in theory, the COVID-19 pandemic could be treated effectively by a series of RdRP inhibitors. However, adenosintriphosphate (ATP) antagonists in general could potentially inhibit many other host enzymes, such as ATPases, protein kinases, and chaperones, and could therefore cause a number of side effects, in the same many as chemotherapeutic agents [39]. Indeed, the RECOVERY-trail treatment arms for ATP-antagonists, such as remdesivir, showed no significant reduction of mortality [40]. For treating COVID-19 in humans, it would be necessary to find far more selective pharmacological agents, namely one which targets a specific host enzyme that is essential for viral infection but not crucial to normal physiology of the host. In human cells, PAK1 RAC/CDC42-activated kinase is the major pathogenic kinase, the abnormal activation of which has been associated with everything from cancer, malaria, and pandemic viral infections to inflammation, immunosuppression, and accelerated aging symptoms [41].

3.4. Ciclesonide and Its Mechanism of Action

Ciclesonide was patented and approved in 2008 in the United States for the treatment of inflammatory lung disease, such as asthma. It is an inhaled corticosteroid that reduces lung inflammation and has been approved for the treatment of asthma and respiratory symptoms. Because of its use in reducing pulmonary inflammation, ciclesonide is of special interest in the context of COVID-19. In order to understand the postulated ciclesonide inhibitory action on COVID-19 in infected human cells, mammalian family kinases called PAKs (RAC/CDC42-activated kinases) which were originally cloned more than 25 years ago were recently further studied [42] [43].

Caffeic acid and its ester, caffeic phenethyl ester occur in propolis (a natural

substance produced by honeybees), the first natural ingredient shown to inhibit RAC and act as a PAK1-blocker [44]. But there are other anti-viral effects in other drugs. The anti-viral effect of remdesivir (IC_{50} around 1 μM of each) was recently confirmed *in vitro* [45]. Furthermore, the expression of LLC2 depends on the coronavirus ACE2-induced CK2/RAS-PAK1-RAF-AP1 signaling pathways. Taken altogether, these observations clearly indicate the PAK1-dependency of coronaviral pathogenesis, and strongly suggest, if not proven clinically as yet, that PAK1-blockers in general might be useful for the treatment of COVID-19. Ciclesonide most probably exerts its anti-inflammatory effect by blocking PAK1 [46].

In order to elucidate the mechanism of action of ciclesonide, glucocorticoids and their recent and current use in clinical practice were reviewed. Glucocorticoids are synthesized in the adrenal cortex and secreted into the blood, where the levels of glucocorticoids fluctuate in a circadian mode [47]. In humans, the naturally occurring glucocorticoid is hydrocortisone (cortisol), which is synthesized from its precursor cortisone. The beneficial effects of glucocorticoids in asthma were first described in 1950. Treatment with glucocorticoids has been consistently shown not only to relieve asthma symptoms, but also enhance bronchial hyperresponsiveness [48]. Corticosteroids (methylprednisolone) were given as treatment during the SARS and Middle East Respiratory Syndrome (MERS) epidemics due to their immunomodulatory effects, which suppress inflammatory responses, but the result of their use showed no perceived benefit and possible deleterious effects [49] [50]. These effects may be mediated in part by modulation of epithelial cell functions, since many *in vitro* and *in vivo* studies, have shown that glucocorticoids are able to modulate the inflammatory functions of bronchial epithelial cells.

Glucocorticoids inhibit the expression of a large number of inflammation-associated molecules, including cytokines, chemokines, arachidonic acid metabolites, and adhesion molecules [51]. These effects predominantly are mediated via the inhibition of NF-κB activity. In contrast, anti-inflammatory mediators, such as NEP and IL-1 receptor antagonists, often are up-regulated by glucocorticoids. The beneficial effects of glucocorticoid in asthma have been demonstrated by *in vivo* studies showing that treatment of asthmatic patients with inhaled glucocorticoids inhibits the airway inflammation and simultaneously improves lung function [52]. Favorable modulation of the immune response is considered one of the possible mechanisms by which corticosteroids might be beneficial or lead to improved clinical outcomes in the treatment of severe acute respiratory coronavirus infections, including COVID-19, SARS, and MERS.

Common to severe cases of coronavirus infections is the presence of hypercytokinemia (also called cytokine storm) and development of acute lung injury or ARDS. Pathologically, diffuse alveolar damage has been found on autopsy [53]. A growing volume of clinical trial data from patients with severe community-acquired pneumonia, ARDS, or septic shock suggest benefit from low-to

moderate dose corticosteroids with respect to mortality and length of stay [54] [55] [56]. A systematic review of (mainly low-dose) corticosteroid trials in severe sepsis and septic shock did not identify any increased risk of gastroduodenal bleeding, superinfection, or neuromuscular weakness; however, an association with an increased risk of hyperglycemia and hypernatremia was noted [57] [58].

Ciclesonide is a parent compound that is converted locally in airways by esterases to produce the active metabolite, desisobutyryl-ciclesonide (des-CIC) [59]. The active metabolite, des-CIC, has a 100-fold greater relative glucocorticoid receptor binding affinity than ciclesonide itself (relative glucocorticoid receptor binding affinities are 1200 and 12, respectively; dexamethasone reference is 100) [60]. If any ciclesonide enters the circulation, it is highly protein bound (99%) and extensively metabolized by liver oxidases, resulting in very low systemic exposure [61]. Ciclesonide is delivered in solution form via a hydrofluoroalkane metered-dose inhaler with a once-daily dosing schedule, which facilitates patient compliance. Clinical studies demonstrate that ciclesonide is as effective as existing *gold standard* inhaled corticosteroids for the control of asthma and has a good safety profile [62]. At its target sites, the lungs, ciclesonide is converted to the active metabolite des-CIC, in a process that is called on-site activation. Pharmacokinetically, high lipophilicity and the formation of a local depot prolong the pulmonary duration of action for des-CIC, explaining the once-daily administration of ciclesonide in clinical practice [63].

Ciclesonide exerts its anti-inflammatory effect most probably by blocking PAK1. Ciclesonide has been shown to block PAK1-dependent replication and pathogenesis *in vitro* [64] Ciclesonide blocks SARS-CoV-2 RNA replication *in vitro* and inhibits cytopathic activity. Ciclesonide demonstrates low cytotoxicity and potent suppression of MERS viral growth. The most commonly used orally administered steroids, cortisone, prednisolone, and dexamethasone do not suppress viral growth, nor did the commonly used inhaled steroid fluticasone. The effective concentration of ciclesonide to block SARS-CoV-2 replication (EC90) was 6.3 μM; ciclesonide 10 mg/kg/day exerts strong suppression of PAK1-dependent growth of lung cancer (A541 cell line) [65]. In addition to its known anti-inflammatory properties, ciclesonide seems to be able to block coronavirus RNA replication [66]. Ciclesonide is used to treat inflammatory diseases, such as asthma and allergic rhinitis [67] [68].

4. Discussion

Systemic corticosteroids were widely used during previous coronavirus outbreaks (SARS and MERS); however, a systematic review of published literature on their use in SARS did not conclude that treatment was beneficial and found some evidence of possible harm [69] [70] [71] [72]. At present, there is no evidence as to whether pre-morbid use or continued administration of inhaled corticosteroids is a factor for adverse or beneficial outcomes in acute respiratory in-

fections due to coronavirus [73] [74] [75]. Schaller *et al.* performed post mortem examinations on 10 patients with verified COVID-19 and found that in 9 patients, infiltrations with ground-glass opacity predominantly in the middle and lower lung fields were detected by chest X-ray, and organized diffuse alveolar damage and SARS-CoV-2 persistence in the respiratory tract were the predominant histopathologic findings and constituted the leading cause of death in patients with and without invasive ventilation [76]. The pulmonary histologic characteristics of COVID-19 resembled those observed in diseases caused by other beta-coronavirus infections such as SARS and MERS [77].

Further data and studies are urgently needed. As a start, it is essential that epidemiological studies of COVID-19 include detailed information on patients' comorbidities and prior medications in order to allow analyses of possible benefits or harms of inhaled corticoid steroids or other therapies [78]. In a recent study, Gralinsky *et al.* [79] demonstrated that complement activation is related to more severe respiratory consequences in SARS coronavirus infections, another hint of the importance of understanding the cascade of events that enhance damage to the host in infections with novel coronaviruses. Most evidence to date show that ARDS is the main cause of death in COVID-19 and that ARDS is the common immunopathological event for SARS-CoV-2 infections, and its predecessors, SARS-CoV and MERS-CoV infections [80] [81]. One of the main mechanisms for ARDS is the cytokine storm, the deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of different pro-inflammatory cytokines; interferons, interleukins, tumor necrosis factor-α, transforming growth factor-β and chemokines [82] [83] [84] [85]. The suggestion by Mehta to consider active immunosuppression as a strategic tool leads to the question as to the appropriate deployment of ciclesonide, for example, whether inhaled ciclesonide should be used early in the disease (and at what dose) and replaced by oral steroids later. However, the window in which oral steroids might be beneficial to patients with COVID-19 is likely narrow compared to that of inhalation steroids, which have documented effect *in vitro* studies.

5. What Is New and Objective

Secondary complications of COVID-19, such as bacterial pneumonia, may require antibiotics [86]. Patients treated with inhalation steroids are at increased risk for bacterial pneumonia [87]. In COVID-19, patient stratification by risk of disease severity has eluded us with the result that hospitals emphasize treatment of the critically ill, while it may be more beneficial in this disease to intervene early. The liberal use of a two-week course of prescribed inhalation ciclesonide as a prophylactic for outpatients with COVID-19 symptoms should be considered. Of course, there is still a risk that some of these outpatients may develop severe respiratory symptoms [88]. But this approach is the gold standard for patients with respiratory syncytial virus infections [89], COPD, and asthma ex-

acerbation [90]. There is also an urgent need to assess the benefits of inhaled corticosteroids for treating COVID-19 patient with and without underlying chronic respiratory disease. Further studies on inhaled steroids would be beneficial and are ongoing [82] [83] [84].

Many of the treatments used in SARS or MERS patients in outbreak situations were not based on clear *in vitro* and *in vivo* model evidence of efficacy, and meta-analyses of treatments failed to show effective therapeutic regimens. In clinical praxis it is routine to treat severe asthma with increased doses of steroids and these recommendations remain unchanged during the pandemic. There have been observations of increased mortality in exacerbations of chronic pulmonary obstructive disease (COPD) in these groups when analyzing COVID-19 mortality data, indicating that the inhalation steroids contribute to increased mortality, according to some authors [69]. Surprisingly, the prevalence of COPD among patients with SARS and COVID-19 appears to be lower than among the general population [70].

The co-occurrence of asthma with obesity, another predictor of poor outcome in COVID-19 patients, places obese patients with asthma at markedly higher risk for worse outcomes [71]. Inhaled corticosteroids use undoubtedly reduces the rate of exacerbations in both asthma and COPD. If people with stable asthma stop or reduce their inhaled corticosteroids inappropriately in response to concerns about immunosuppression and worries about developing COVID-19, they may be at significant risk of having an exacerbation [72]. Approximately 40% - 60% of COPD and up to 80% of asthma exacerbations occur due to viral infections, including common coronaviruses [73]. Approximately 25% of patients admitted to the hospital developed ARDS a median of 10.5 days after symptom onset [86]. Sadly, patients with underlying lung disease hospitalized with COVID-19 have worse outcomes [87] [88] [89]. In people with COPD, inhaled corticosteroid use is associated with a higher prevalence of pneumonia and a change in the lung microbiome, although not a change in respiratory virus detection [90].

6. Conclusion

Dexamethasone reduces mortality in severe COVID-19 patients requiring ventilator treatment. Less is known about steroid treatment in milder forms of COVID-19. Ciclesonide is a safe and effective inhaled steroid with few side effects. As ciclesonide is inhaled, it is metabolized locally in the most affected critical organ of infected patients. Its metabolites have far higher receptor affinity than that of dexamethasone, so it is reasonable to assume a greater clinical effect. Therefore, randomized controlled trials are welcome to elucidate the role of inhaled corticosteroids in COVID-19 in addition to their use in patients with preexisting conditions.

Acknowledgements

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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