Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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REVIEW ARTICLE

Role of Systemic and Nasal Glucocorticoid Treatment in the Regulation of the Inflammatory Response in Patients with SARS-Cov-2 Infection

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The Chinese outbreak of SARS-CoV-2 during 2019 has become pandemic and the most important concerns are the acute respiratory distress syndrome (ARDS) and hyperinflammation developed by the population at risk (elderly and/or having obesity, diabetes, and hypertension) in whom clinical evolution quickly progresses to multi-organ dysfunction and fatal outcome. Immune dysregulation is linked to uncontrolled proinflammatory response characterized by the release of cytokines (cytokines storm). A proper control of this response is mandatory to improve clinical prognosis. In this context, glucocorticoids are able to change the expression of several genes involved in the inflammatory response leading to an improvement in acute respiratory distress. Although there are contradictory data in the literature, in this report we highlight the potential benefits of glucocorticoids as adjuvant therapy for hyperinflammation control; emphasizing that adequate dosage, timing, and delivery are crucial to reduce the dysregulated peripheral-and neuro-inflammatory response with minimal adverse effects. We propose the use of the intranasal route for glucocorticoid administration, which has been shown to effectively control the neuro-and peripheral-inflammatory response using low doses without generating unwanted side effects.

Key Words: Intranasal delivery, COVID-19, Inflammation, Glucocorticoids, Immunity.

Introduction

By June 16, the pandemic coronavirus disease 2019 (COVID-19) is affecting 214 countries and territories around the world; there are 8,349,950 infection cases, 448,959 deaths, and a mortality rate of 3.4% (1,2). COVID-19 is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which has a wide spectrum of clinical forms that include high fever, chills, cough, anosmia, and breathing difficulty (fewer common symptoms are diarrhea, myalgia, fatigue, and hemoptysis). Although some infected individuals do not show any symptom and the majority of cases present mild respiratory illness, some infected people can develop severe pneumonia, acute respiratory distress syndrome (ARDS), multiple organ failure, and ultimately death (3).

Patients are firstly admitted to a hospital with a median of 7 d after the onset of symptoms (3). As for June 16, 2020, there were 154,863 infected persons in Mexico (32% hospitalized and 68% ambulatory) and 18,310 deaths (DGE, Dirección General de Epidemiología, https://www.gob.mx/salud/documentos/datos-abiertos-152127.). Among the hospitalized patients, nearly 9% require intensive care treatment for respiratory assistance and mechanic ventilation. Severe COVID-19-associated complications resulted from exacerbated and uncontrolled inflammation; leading to multiple organic dysfunctions. This review provides an outlook on the currently available information for the SARS-CoV-2 infection; seeking to analyze the relevance of dysregulated inflammation and neuroinflammation of the COVID-19 pathogenesis. Moreover, this review highlights the potential benefits of glucocorticoids as adjuvant therapy focused on adequate dosage, timing, and delivery as crucial actions to improve clinical outcome by reducing the dysregulated peripheral and neuro inflammation. The

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control of the neuroinflammation represents a challenge because glucocorticoids (GC) intravenously administered requires high systemic doses to reach therapeutic levels in the Central nervous system CNS). Herein, the use of the intranasal route for GC administration is proposed as this route allows the direct entrance of the drug to the brain via the olfactory system and trigeminus, bypassing the brain-blood barrier. The intranasal administration allows the control of the neuroinflammation using very low doses of GC minimizing non-desirable effects (4,5). Additionally, this route allows effective entry of GC into the respiratory system and can also effectively control the exacerbate inflammation at this level.

Pathogenesis

Virus-Mediated Lesion

The nasal cavity is an important gate for SARS-CoV-2 entry; in fact, the virus is able to invade olfactory and respiratory epitheliums through the interaction of the spike (S) protein and the angiotensin-converting enzyme 2 (ACE2) receptor, which involves cleavage of the S protein most likely by the cell surface protease TMPRSS2 (Figure 1A). The ACE2 receptor has been found widely distributed on hepatic tissues and the human upper airway (including nasal respiratory epithelium, basal, and ciliated cells), intestinal, renal, cardiac, and nervous systems (glial cells and neurons) (Figure 1B) (6−13).Therefore, the virus can spread into lungs where it causes pneumonia and subsequently disseminate to several organs and systems causing different degrees of damage; further increasing the inflammatory response.

Another route of entry for the virus in the central nervous system is through olfactory and trigeminal nerves (14,15); as described for other human CNS viral infections such as the poliomyelitis virus. This situation has also been described for other animal models (16). Findings of altered smell sense in the early stages of COVID-19 support this possibility, while affectation of the CNS will manifest by acute cerebrovascular disease, encephalitis, and epilepsy;

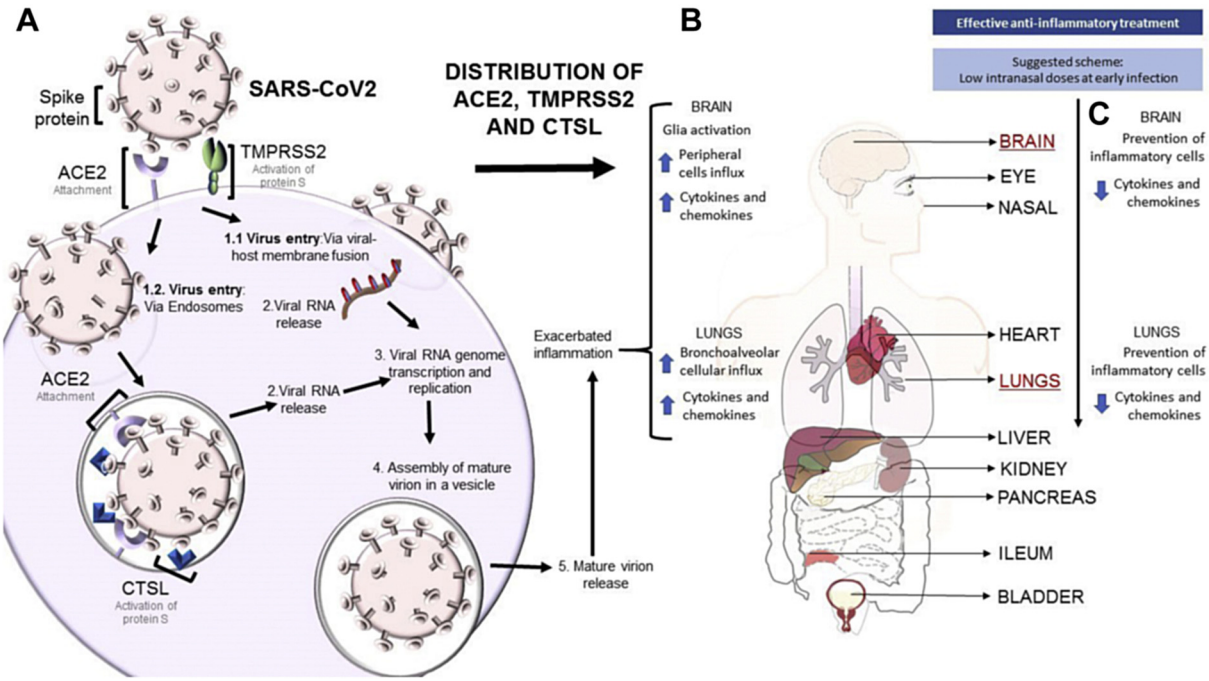

Figure 1. SARS-CoV-2 pathogenesis. SARS-CoV-2 cell entry depends on ACE2, TMPRSS2, and CTSL (A) The SARS-CoV-2 virus uses two ways to enter the host cells: (1.1) Via host membrane fusion through the binding of the viral spike proteins (S) to the ACE2 (angiotensin-converting enzyme 2) receptor, which is co-expressed with the serine protease TMPRSS2 (type II transmembrane serine protease), that allows the priming of the viral protein S, initiating the fusion of the viral membrane with the host membrane. (1.2) Via endosomes. In this pathway the endosomal protease CTSL (cathepsin L) primes the viral protein S. Then, (2) viral RNA is released into the host cell. Once (3) viral RNA transcription and replication occurred, (4) the virion assembly takes place, small vesicles are released from the Golgi apparatus containing (5) virions that are released from the infected cell through exocytosis. (B) The receptors and proteases essential for SARS-CoV-2 infective cycle are present in a wide variety of tissues and cell types: brain (glial cells and neurons), eye (corneal epithelium), nasal (globet, basal and ciliated cells), heart (myocyte, pericyte), lungs (secretory, basal and multiciliated cells), liver (cholangiocytes), pancreas (ductal epithelium), kidney (proximal tubule cells), ileum (fibroblast, endothelial, and epithelial enterocytes), bladder (fibroblast, and epithelial cells), among others. (C) SARS-CoV-2 infection can induce a host immune response that leads to exacerbated inflammation not only in the respiratory system but at the systemic level and in the central nervous system. The common mechanisms supporting such inflammatory state include enhanced cellular influx with the subsequent cytokine and chemokine secretion, which are in part due to pyroptosis induced by the pathogen. An effective anti-inflammatory treatment might comprise the administration of corticosteroids at stage 2 just before the appearance of cytokine storm. Pulmonary insufficiency is likely associated to impairment of the central respiratory system provoked by the viral-induced neuroinflammatory response. Therefore, IN administration of low GC doses may provide better therapeutic effects avoiding the undesired effects of the high GC doses typically administered parenterally, such as the increase of viral load. A clinical trial to assess this proposed therapeutic scheme is under planning.

frequently observed in patients with severe forms of COVID-19 (9,14,15). In addition, in later stages of the infection (characterized by general damaged endothelium) the virus can also reach the CNS through this via (17).

Inflammatory and Neuroinflammatory-Mediated Damage

Higher systemic levels of IL-6, IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1α, and (TNF-α) have been observed in COVID-19 patients (18,19). In addition, increased IL-1β levels are believed to be a consequence of pyroptosis favored by the virus-mediated antagonism of the interferon (IFN) response; with an overall promotion of aberrant inflammatory responses (20). Another mechanism likely involved in lung inflammation is the antibody-dependent enhancement mediated by pre-existing antibodies to other coronaviruses or anti-S protein antibodies induced earlier in the infection. The binding of antibody−virus immune complexes activating Fc receptors on alveolar macrophages could be involved in the induction of pro-inflammatory factors and complement activation (21−23). This uncontrolled and sustained hyperinflammation in the respiratory system results in severe pneumonia; the main condition that leads to severe acute respiratory distress syndrome (SARD) often requiring weeks of mechanical ventilation. This situation leads to high mortality, 71 to 96% of patients with severe pneumonia die according to data available in Mexico.

Exacerbated inflammation also affects functionality of the vascular endothelium with an altered permeability that favors cell migration and arterial vasoconstriction. Altered endothelium is also involved in the development of a disseminated intravascular coagulation in patients with severe COVID-19 (24).

Respiratory dysfunction is mediated by exacerbated lung inflammation coupled with dysfunction of respiratory control centers from the brain (9,25,26). Indeed, SARS-CoV-2 may enter neurons and glial cells resulting in cellular stress and injury and the expression of Damage-associated molecular patterns (DAMPs), which promote the strong release of cytokines (cytokines storm), excessive production of reactive oxygen species (ROS), and the activation of microglia; favoring the migration of inflammatory peripheral cells through a damaged brain blood barrier. Sustained neuroinflammation may exacerbate neuron injury, therefore spreading damage and contributing towards central respiratory failure. The frequent finding of neurological manifestations in COVID-19 patients strongly supports this possibility (17). Hence, it is essential not only to treat the peripheral inflammatory response, but the neuroinflammation to reduce central dysfunctions.

Risk Factors for Severity and Mortality

Comorbidities such as aging, hypertension, diabetes, obesity, and cardiovascular disease are the main COVID-19 factors predicting poor outcomes. The exacerbated inflammation status (27) is a common denominator of all these conditions underlying, at least in part, pathogenesis in SARS-CoV-2 infection. In older people immune homeostasis loosens and inflammatory responses become less regulated. Severe oxidative stress, DNA damage, cytokine response dysregulation, and reduced autophagy are all involved in the ‘‘inflammaging’’ of elderly people (28). Hypertension is considered a pro-inflammatory disease often associated with endothelial dysfunction. Obesity and diabetes are also associated with metabolic dysregulation and a chronic low-grade of inflammation (29) triggered by antigen-presenting cells involved in recognizing damaged and death cells; mediated by increased oxidative stress (30). Finally, cardiovascular diseases are associated with systemic metabolic and inflammatory signals (chronic inflammatory state affecting immune cell response), which seem to be relevant for a poor outcome (31).

COVID-19 Clinical Stages

Currently several clinical stages have been described for COVID-19 (32). These stages are distinguished by the factor that is mainly involved in pathogenicity. The following staging was proposed: the first stage (mild, early infection) occurs at the time of inoculation and early establishment of the disease. Symptoms are very mild and nonspecific, while virus replication is intense. Most of the patients will only present this stage and their recovery will be excellent. In the second stage (moderate, pulmonary involvement without (2A) or with hypoxia) (2B) patients present pneumonia that can be diagnosed by radiological tools. They frequently have an increase of systemic inflammatory markers; although this reaction is mild. Virus is still present, but its burden is decreasing. A small group of patients will then pass to stage 3 (severe); characterized by severe ARDS and systemic hyperinflammation and neuroinflammation with the risk of multi-organ failure. Here, the virus is nearly undetectable and pathogeny is almost exclusively driven by the inflammatory response (cytokines storm) (33).

Controlling the Exacerbated Inflammation and Neuroinflammation

An uncontrolled inflammatory response promotes detrimental events in the host dysregulated inflammatory response also affects the coagulation and the fibrinolytic cascade promoting a prothrombotic state that contributes to cardiovascular disorders and hypertension, as well as hematological disorders observed in COVID-19 patients (34). In this context, several drugs are currently used to control the exacerbated inflammation immune. Glucocorticoids (GC) are among these since it is one of the commonest and powerful anti-inflammatory drugs. Three critical point must be considered to use GC to control the dysregulated inflammatory response (Figure 1C): the timing, the dose, and the route of administration. First, GC will not be

Table 1. Some experiencies in sars cov using glucocorticoids to control the exacerbated inflammatory response

Glucocorticoid employed	Dexamethasone equivalence	Result	Number of patients	Reference
Methylprednisolone				
Non critical patients received a daily dose mean of MP of 105.3 ± 86.1 mg	19.7 ± 16.1 mg daily	147 out of 249 non-critical patients received GC (59%). All of these patients lived. 121 out of 152 critical patients (79.6%) received GC. 25 critical patients died, from them 18 were treated with MP.	401	(37)
Critical patients received a daily mean dose of 133.5 ± 102.3 mg.	25 ± 19.2 mg daily	Less fatality, lower hospital stance and no significant infections in lower airways were found in critical patients that received MP		
Methylprednisolone				
80−160 mg/d (24 patients), 3 weeks	15−30 mg/d	The high dose (1000 mg/d) reduced the levels of CD4, CD8 and CD3 T cells, increased glucose, reduce albumin and promoted secondary infections that worsened the disease.	30	(38)
1000 mg/d (5 patients)	187.5 mg/d			
Methylprednisolone		17 patients responded to the combined treatment (Ribavirin and methylprednisolone.)		
3 mg/kg daily (IV/5 d) and 2 mg/kg IV/5 d	0.6 mg/kg			
Followed by	0.4 mg/kg			
Prednisosne				
1 mg/kg orally/5 d	0.2 mg/kg			
An additional pulse of MP (1 g/d) for 2 d IV was given to severe cases.	0.1 mg/kg	11 patients required the additional pulse of MP as a severe disease was developed. No patient required intubation nor mechanical ventilation; High dose corticosteroids produced no severe complications	28	(39)
Methylprednisolone				
≥500 mg/d (n = 17)	≥93.7 mg/d	No significant differences in intubation and in intensive care unit admission or mortality rates were found between the two treatment groups although patients with lower doses of MP had significantly less oxygen requirement, better radiographic outcome, and less likelihood of requiring rescue PS therapy.	72	(40)
<500 mg/d (n = 55)	<93.7 mg/d			
Low dose of GC				
Prednisone				
(0.5−1 mg/d) for 3−4 d	2.51 mg/d	25 patients (18.1%) responded to ribavirin and low-dose corticosteroid. High-dose methylprednisolone was used in 107 patients, of whom 95 patients (88.8%) responded favorably.	138	(41)
In non-responders High dose of MP				
Methylpredinosole				
(500 mg/d) for 3 d	93.7 mg/d	It was concluded that high-dose pulse methylprednisolone during the clinical course of a SARS outbreak was associated with clinical improvement.		
Hidrocortisone				
10 mg/kg/d	0.4 mg/kg/d	An increase in the 30 d mortality associated with high-dose steroids	218	(42)
Pulse of Methylprednisolone in non-responders				
2−3 pulsing doses of 500−1,000 mg a day intravenously	93.7−187.5/d			

employed from the beginning of the infection, the time at which the inflammation favors the host. Second, it must be given in a low dose to minimize negative side effects. The intranasal delivery would allow direct access of GC to the central nervous system thereby controlling the sustained neuroinflammation provoked by damage to infected CNS cells that provoke fatal central respiratory and cardiac failure of COVID-19 patients. In addition, intranasal GC efficiently reach the respiratory system and control peripheral inflammation (4).

Controlling the Inflammation and Neuroinflammation During COVID-19: How and When

Considering that severe complications associated with COVID-19 mainly result from exacerbated and

Table 2. Clinical trials performed using glucocorticoids on SARS-CoV-2 patients

Intervention and results	Intervention	References
Patients with rheumatic diseases on long immunosuppressive therapy should not stop GC during COVID-19 infection, small doses may be used.	Prednisone 5−7.5 mg/d [a]DEX equivalent dose of 1.9−3.7 mg/d	(40)
A retrospective, observational study where comorbidities and treatments were collected and analyzed in patients with and without elevation of troponin T levels.	Methylprednisolone 40−80 mg/d [a]DEX equivalent dose of 7.5−15 mg/d	(41)
An open-labeled, randomized, controlled trial	Methylprednisolone i.v. 1−2 mg/kg/d for 3 d, [a]DEX equivalent dose of 0.2−0.3 mg/kg/d	(42), ChiCTR2000029386
A multi-center, randomized, control study to evaluate the efficacy and safety of glucocorticoid in combination with standard care for COVID-19 patents with SAR failure.	Methylprednisolone 40 mg each 12 h for 5 d [a]DEX equivalent dose 7.5 mg each 12 h Other: Standard care Sample size: 80	NCT04244591 https://clinicaltrials.gov/ct2/show/NCT04244591
This study was designed to investigate if prophylactic treatment with short term steroids administered to high risk Covid-19 patient might prevent cytokine storm and progression to respiratory failure.	Methylprednisolone 80 mg IV bolus injection will be given daily x 5 d starting upon day 1 of admission to hospital.	NCT04355247 https://clinicaltrials.gov/ct2/show/NCT04355247
This study evaluates the use of anti-inflammatory drugs used at the time they start hyperinflammation episodes could improve symptoms and prognosis of SARS-CoV-2 positive patients and prevent their progression sufficiently to avoid their need for be admitted to an Intensive Care Unit.	Siltuximab. A single dose of 11 mg/kg administered by intravenous infusion. Methylprednisolone 250 mg/24 h for 3 d followed by 30 mg/24 h for 3 d. If the patient is taken lopinavir/ritonavir, the dose will be 125 mg/24 h for 3 d followed by 15 mg/24 h for 3 d.	NCT04329650 https://www.smartpatients.com/trials/NCT04329650
Evaluation of a new strategy for treatment of COVID-19 which consists of Levamisole as immunostimulator, Formoterol + Budesonide inhaler can be used in this protocol.	Levamisole (50 mg every 8 h) + Budesonide + Formoterol inhaler has to be inhaled 1−2 puff every 12 h Lopinavir/Ritonavir (2 tablets every 12 h) + hydroxychloroquine (200 mg single dose)	NCT04331470 https://clinicaltrials.gov/ct2/show/NCT04331470
Measurement of CoVid-19 pneumonia (CVP) and inflammation will be made using a patented method (FMTVDM #9566037 and adjunct USPTO submissions deemed covered by USPTO under the original patent #9566037).	Methylprednisolone, Hydroxychloroquine, Azithromycin, Doxycycline, Clindamycin, Primaquine, Remdesivir, Tocilizumab, Interferon-α2B, Losartan, Convalescent Serum FMTVDM Planar, SPECT, PET	NCT04349410 https://clinicaltrials.gov/ct2/show/NCT04349410
This study will evaluate the benefit, safety and tolerability of corticosteroid therapy to reduce the rate of subjects hospitalized for Covid-19 viral pneumonia.	Prednisone (oral) for 10 d (0.75 mg/kg/d for 5 d, then at 20 mg/d for 5 more d) The control group will receive standard of care. No corticosteroid therapy can be prescribed in this group.	NCT04344288 https://clinicaltrials.gov/ct2/show/NCT04344288
The aim of this study is to examine the effects of dexamethasone on hospital mortality and on ventilator-free days in patients with moderate-to-severe ARDS due to confirmed COVID-19 infection.	Dexamethasone (20 mg/iv/daily/from Day 1 of randomization for 5 d, followed by 10 mg/iv/daily from Day 6−10 of randomization)	NCT04325061 https://clinicaltrials.gov/ct2/show/NCT04325061
The main objective of this study is to assess the impact of dexamethasone on overall mortality at day 60 after randomization in patients admitted in ICU for severe COVID-19 infection. In non-mechanical ventilation (MV) patients, the additional objective is to assess whether oxygen support based on either HFNO or CPAP modality in COVID-19 related AHRF reduces the need for mechanical ventilation at day 28.	Dexamethasone 20 mg/5 mL, solution for injection. Placebo: NaCl 0,9% Procedure: conventional oxygen Procedure: CPAP Patients assigned to the CPAP plus oxygen group will receive periods of CPAP in addition to the standard treatment. Procedure: HFNO	NCT04344730 https://clinicaltrials.gov/ct2/show/NCT04344730
Evaluated the early administration of corticosteroids in ARDS patients.	Dexamethasone and Hydroxy-chloroquine. Patients will receive Dexamethasone (20 mg IV) for 15 min once a day for 5 d (D1 to D5), then at a rate of 10 mg/d from D6 to D10. If the patient is extubated before the 10th day, he will receive his last dose of DXM before. Patients included in the Hydroxy-chloroquine group will receive 200 mg x 3/day enterally from J1 of the HCQ for 10 d. If the patient is extubated before the 10th day, he will receive his last dose of HCQ before.	NCT04347980 https://clinicaltrials.gov/ct2/show/NCT04347980
This study was designed to compare the efficacy of different hormone doses in the treatment of 2019-nCoV severe Pneumonia.	Methylprednisolone (<40 mg/d intravenous drip for 7 d or 40~80 mg/d intravenous drip for 7 d).	NCT04263402 https://clinicaltrials.gov/ct2/show/NCT04263402

(*continued on next page*)

Table 2 (*continued*)

Intervention and results	Intervention	References
The present study will evaluate the effective-ness of dexamethasone compared to control (no corticosteroids) in ventilator-free days at 28 d in patients with moderate and severe ARDS due to SARS-CoV2 virus in Brazil.	Dexamethasone 20 mg IV 1x/day for 5 d, followed by 10 mg IV 1xd for 5 d + standard treatment (according to the treatment protocol for 2019-nCoV infection). Standard treatment (according to the treatment protocol for 2019-nCoV infection).	NCT04327401 https://clinicaltrials.gov/ct2/show/NCT04327401
This study will evaluate the use of Methylprednisolone pulses and Tacrolimus in hospitalized severe COVID-19 lung injury patients might have a positive clinical effect.	Tacrolimus. The necessary dose to obtain blood levels of 8−10 ng/mL Methylprednisolone 120 mg daily for 3 consecutive d	NCT04341038 https://clinicaltrials.gov/ct2/show/NCT04341038
The clinical trial aimed at investigating if the addition of inhaled corticosteroids (budesonide) reduces treatment failure (defined as a composite variable by the initiation of treatment with high flow-O2 therapy, non-invasive or invasive ventilation, systemic steroids, use of biologics (anti IL-6 or anti IL-1) and/or death) according to hospital standard of care guidance at day 15 after initiation of therapeutic intervention.	Inhaled budesonide adding to standard of care for pneumonia in COVID19 positive patients	NCT04 https://www.clinicaltrials.gov/ct2/show/NCT04355637355637
This study will evaluate the use of Methylprednisolone administered based on CRP-guided protocol	Methylprednisolone will be administered based on CRP-guided protocol outlined under ''Biomarker-adjusted steroid dosing''. CRP levels will be drawn with early morning labs and used to determine the steroid dosing for the day. Other: Usual Care.	NCT03852537 https://clinicaltrials.gov/ct2/show/NCT03852537
The aim of this study is the comparison of two groups of patients SARS-CoV-2 positive with severe acute respiratory syndrome: consecutively treated with low prolonged doses of methylprednisolone	Methylprednisolone given at low prolonged dose infusion after initial 80 mg iv bolus at admission followed by 80 mg in 240 cc 0.9% saline administered iv at 10 cc/h speed for at least 8 d or more until PCR < 20 mg/L and/or P/F > 350. Then methylprednisolone 16 mg BID os slowly tapering until PCR normal range +/− normal range and P/F > 400. Control group will be treatment without any administration of methylprednisolone and other corticosteroids.	NCT04323592 https://clinicaltrials.gov/ct2/show/NCT04323592

[a]The use of several GC in different studies were converted to dexamethasone (DEX) equivalent doses in order to compare the different doses employed in those studies in terms of dexamethasone.

uncontrolled peripheral- and neuro-inflammation, one widely employed therapeutic approach is GC administration (35). In fact, synthetic GC are one of the most potent anti-inflammatory therapeutic drugs commonly used in the treatment of an array of inflammatory disorders (36).

The experience of employing corticosteroids to treat the exacerbated inflammation in patients with SARS during 2002−2004 may orientate the use of these steroids in the present COVID-19 pandemic disease. Similarities in the inflammatory response are found between SARS-CoV-1 and SARS-CoV-2. Several protocols to treat the inflammatory response in SARS and deal with the virus or secondary bacterial infections were assayed (Table 1), however many of them were not randomized controlled trials. The treatments included an antiviral drug (Ribavirin) or two or more antibiotics (i.e. levofloxacin or levofloxacin plus azithromycin or clarithromycin plus amoxi-clav) combined with steroids (43,44,38-42). Most of these studies employed a 2 corticosteroid schedule with methylprednisone (MP) and prednisone and a pulse of MP, which was given if clinical condition, chest radiograph, or oxygen saturation worsened and lymphopenia persisted. The general conclusion of these studies was that the inclusion of the corticosteroid therapy for the treatment of SARS-affected patients resulted in better response when administered appropriately: several days after the onset of the symptoms (stage 2) in medium or low doses and for a moderate period. However, in some studies, low levels of T cells (CD4+ and CD8+) or high viral load were reported, but no association with disease severity was reported. In one study an increase in 30 d mortality was found, which was associated with the administration of high-dose steroids. Nonetheless, in this study no strictly matching of SARS cases was performed.

Upon most of viral infections, the initial inflammatory reaction is triggered as an attempt to control the infection and promote the development of an efficient immune response. Therefore, inhibition of inflammatory/immune responses in this phase may favor viral replication. This was shown in a study including patients affected by SARS-CoV-1 who received GC early after infection resulting in

increased viral load (45). In contrast, in a recent large multicenter and randomized study conducted in patients with moderate to severe ARDS, administration of dexamethasone (0.25 mg/kg) reduced mortality and the time needed for mechanical ventilation (46).

There is little experience in using GC on SARS-CoV-2 to date (47-49) as shown in Table 2. For this reason the World Health Organization (WHO) has pointed the need of randomized clinical trials for the use of GC to determine safety and efficacy (https://www.who.int/blueprint/priority-diseases/keyaction/Global_Research_Forum_FINAL_VERSION_for_web_14_feb_2020.pdf ? ua = 1). Therefore, there are numerous clinical studies currently underway (Table 2).

Certainly, the decision of administrating GC in SARS-CoV-2 infected patients will also depend on their clinical history accounting a compromised immunological condition, as potential risk can be developed in those in which a GC administration can increase a previous immunosuppressive immune response.

Taken together, these precedent studies provide crucial information on three fundamental aspects to be considered for modulation of inflammation during COVID-19: the time in which GC are recommended to start, the effective dose to control inflammation with minimal negative side effects, and the delivery route selected to reach the CNS (Figure 1C).

Conclusions and Perspectives

The SARS-CoV-2 infection dramatically illustrates the double edge of inflammation. While it is essential to contain infection and develop an adaptive immune response that increases the efficiency to deal with the virus; its dysregulation and exacerbation can produce negative results that include a fatal outcome for the patient. The analysis presented in this review emphasizes the relevance of controlling inflammation during stage 2 of infection, allowing the establishment of adaptive immunity that prevents the appearance of severe symptoms. Based on the available evidence, we propose that the optimal time to start a low-dose GC-based treatment is at least 5 d after the onset of symptoms. It would be very important to define inflammatory markers to standardize the timing of GC administration. Unfortunately, due to the high number of patients and the difficulties to perform laboratory tests in all the settings, clinical criteria are more feasible to be used now. It is also important to emphasize the relevance to control not only the dysregulated peripheral inflammatory response, but also the neuroinflammation to reduce cerebral dysfunctions. In order to increase the efficacy of reaching the central nervous and respiratory systems, we propose the use of the intranasal route for GC administration. This route avoids the requirement of high GC doses to reach the CNS. The available experimental evidence derived from a mice model of sepsis supports that this route is more efficient than the intravenous route to control both the exacerbated peripheral- and neuro-inflammatory responses (4,5). Moreover, since lower doses are administered when compared to the parenteral scheme the negative collateral effects are reduced. A clinical protocol is being reviewed to begin evaluation of intranasal GC at low doses in COVID-19 hospitalized patients. The treatment will begin when shortness of breath appears, usually in the second week of illness; seeking to prevent the progress to hypoxemia.

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Conflict of interest

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