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# A critical evaluation of glucocorticoids in the management of severe COVID-19

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## ABSTRACT

The viral infection by SARS-CoV-2 has irrevocably altered the life of the majority of human beings, challenging national health systems worldwide, and pushing researchers to rapidly find adequate preventive and treatment strategies. No therapies have been shown effective with the exception of dexamethasone, a glucocorticoid that was recently proved to be the first life-saving drug in this disease. Remarkably, around 20 % of infected people develop a severe form of COVID-19, giving rise to respiratory and multi-organ failures requiring subintensive and intensive care interventions. This phenomenon is due to an excessive immune response that damages pulmonary alveoli, leading to a cytokine and chemokine storm with systemic effects. Indeed glucocorticoids' role in regulating this immune response is controversial, and they have been used in clinical practice in a variety of countries, even without a previous clear consensus on their evidence-based benefit.

## 1. Introduction

The ongoing pandemic of Coronavirus Disease 2019 (COVID-19), caused by the novel Severe Acute Respiratory Syndrome-Coronavirus (CoV)-2 (SARS-CoV-2), was declared a Public Health Emergency of International concern on January 30, 2020 by the World Health Organization (WHO<sup>[a]</sup>). One month before, pneumonia of unknown origin was detected in Wuhan, China, and was first reported to the WHO Country Office in China. This viral infectious disease is characterized by a high mortality, principally caused by a respiratory failure due to a severe cytokine and chemokine storm, an exaggerated immune response of the host aimed at preventing the invasion of the pathogen. Such a strong reaction is considered responsible for the pathogenesis of the host tissue damage (i.e., of pulmonary alveoli and of pro-inflammatory systemic effects), leading to the principal severe clinical manifestations of COVID-19 (i.e., respiratory and multi-organ failure

(MOF)).

Indeed, around 20 % of infected patients develop an Acute Respiratory Distress Syndrome (ARDS) [1,2] (Fig. 1), which is thought to be linked to the massive release of pro-inflammatory cytokines (i.e., interleukin (IL)-1 $\beta$  [IL-1 $\beta$ ], IL-2, IL-6, IL-7, IL-8, tumor necrosis factor- $\alpha$  [TNF- $\alpha$ ] and chemokines (C-X-C motif ligand 10 [CXCL10] and CC motif ligand 2 [CCL2]), further giving rise to MOF [3,4]. Risk factors for the development of ARDS in COVID-19 were: older age, neutrophilia, organ dysfunction and coagulation dysfunction [5]. The entire phenomenon is named Cytokine Release Syndrome (CRS), or Systemic Inflammatory Response Syndrome (SIRS), or Secondary haemophagocytic lymphohistiocytosis (SHLH). The management of this cytokine and chemokine storm during COVID-19 represents a crucial and controversial point [6], considering that the use of immune suppressive drugs such as glucocorticoids (GCs) can either inhibit the tissue damage and at the same time curb the cell-mediated immunity (i.e., reducing

**Abbreviations:** ARDS, Adult Respiratory Distress Syndrome; CAP, Community Acquired Pneumonia; CCL2, CC motif ligand 2; COVID-19, Coronavirus Disease 2019; CRS, Cytokine Release Syndrome; CXCL10, C-X-C motif ligand 10; DX, dexamethasone; GC, glucocorticoid; GCR, glucocorticoid receptor; GM-CSF, Granulocyte Monocyte-Colony Stimulating Factor; ICU, Intensive Care Unit; IL, interleukin; IV, intravenous; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; MP, methylprednisolone; MOF, multi-organ failure; O<sub>2</sub>, oxygen; RCT, Randomized Controlled Trial; SARS-CoV-2, Severe Acute Respiratory Syndrome-Coronavirus-2; SHLH, Secondary haemophagocytic lymphohistiocytosis; SIRS, Systemic Inflammatory Response Syndrome; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; ULN, upper limit of normal; WHO, World Health Organization

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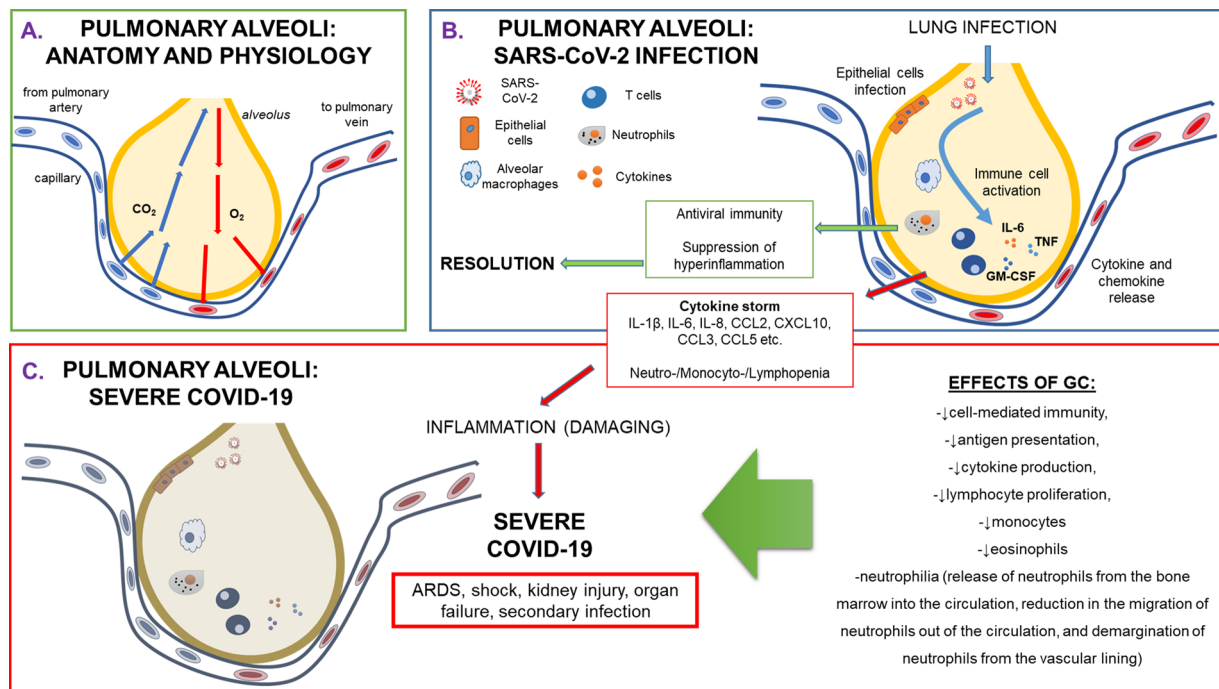


Fig. 1. Physiology and pathophysiology of pulmonary alveoli during SARS-CoV-2 infection.

(A) Anatomy and physiology of healthy pulmonary alveoli, representing small air spaces in the lungs where carbon dioxide leaves and oxygen enters the blood. During inhalation air enters the lungs, travels through bronchi, bronchioles and then flows into approximately 300,000,000 alveoli. During exhalation, the carbon-dioxide-laden air is forced out of the alveoli through the same passageways. (B) Pathophysiology of pulmonary alveoli during SARS-CoV-2 infection. Infection of the novel Coronavirus, named SARS-CoV-2 creates an epithelial damage, followed by an immune response that is generated by a cytokine and chemokine release. This could lead to immune cell activation that might give rise to either resolution and severe COVID-19 with the consequent development of ARDS and of multi-organ failure. (C) Severe COVID-19: immune biological aspects. A sustained cytokine storm generates an inflammation that causes damage to the alveolar epithelium, giving rise to ARDS, shock, kidney injury, other organ failure and secondary infection.

Legend: ARDS: Adult Respiratory Distress Syndrome; CCL: C-C motif chemokine ligand; CXCL: C-X-C motif chemokine ligand; CO<sub>2</sub>:carbon dioxide; COVID-19: CoronaVirus Disease-19; GC: glucocorticoid; GM-CSF: granulocyte-monocyte colony stimulating factor; IL: interleukin; TNF: tumor necrosis factor.

antigen presentation, lymphocyte proliferation, etc.) (Fig. 1) [7].

Aims of this narrative review are: to provide a brief synthesis of the rationale for GC use in the management of patients with COVID-19, their principal pharmacological characteristics, their role and the ongoing clinical trials in this setting.

## 2. Glucocorticoids and COVID-19

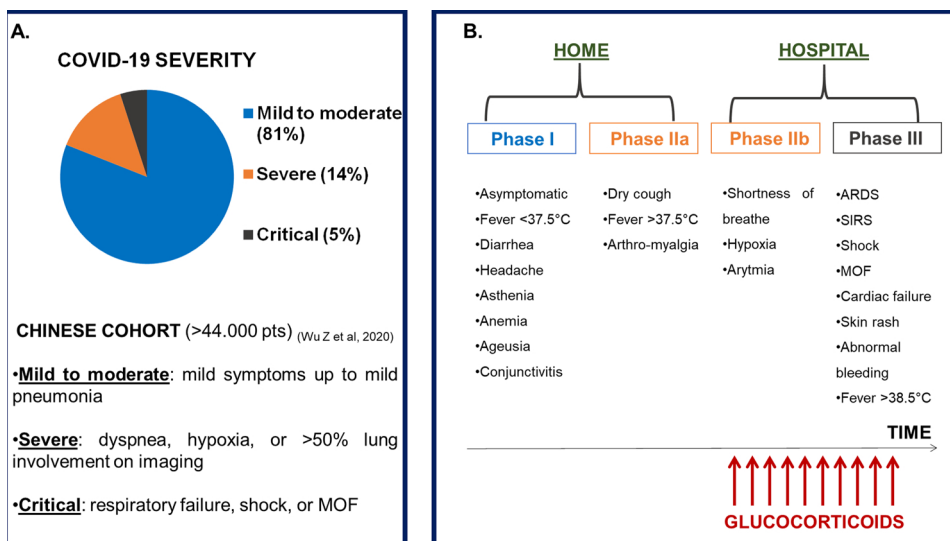
Faced with the complex scenario of severely ill patients with COVID-19, a variety of protocols employing complementary treatments (i.e., anti-viral, anti-malarial and anti-rheumatic agents, serine protease inhibitors, IL blockers and low-molecular-weight heparin (LMWH) [8]) have been developed in various countries, some of them using GCs for the treatment of hospitalized patients with phase IIb-III COVID-19 [9,10] (Fig. 2). The crucial point here is that GCs might be helpful in preventing the alveolar/pulmonary damage induced by the cytokine and chemokine storm. Although GCs are used in this situation as immune suppressants (i.e., leading to an inhibition of cytokine production), they potentially cause delay in the clearance of the virus and impair lymphocyte proliferation, etc. [10,11] (Fig. 1). Nevertheless, in the past, GCs have been used in the management of ARDS caused by Middle East Respiratory Syndrome (MERS)-CoV[12] and SARS-CoV [13], both characterized by a histological pulmonary inflammation and by a diffuse alveolar damage [14] (Fig. 1). However, there was no consensus in the literature that the treatment with GCs could be beneficial in the management of COVID-19, considering the potential delay in the clearance of the virus, but also the increase of the risk of secondary infections and adverse effects (i.e., hyperglycemia, psychosis, and avascular necrosis), and considering that the effects on patients' outcome were not that clear [8,12,13,15]. Recently, results from a

randomized trial were publicly announced, revealing that low dose dexamethasone (DX) helped save the lives of seriously ill patients with COVID-19<sup>[b]</sup>, cutting the risk of death by a third for patients on ventilators and by a fifth for those on oxygen (O<sub>2</sub>) therapy.

## 3. Glucocorticoids: principal mechanisms of action

The mechanisms of action of GCs are characterized as: 1) genomic and 2) non-genomic, as summarized in Fig. 3. The genomic mechanism of action is mediated by the GC receptor (GCR) that generates the majority of anti-inflammatory and immunosuppressive effects. GCR is localized within the cytoplasm, and the complex generated after its binding with the GC translocates into the nucleus, where it inhibits the transcription of the genes involved in the activation of leukocytes and in the regulation of the function of epithelial, stromal and endothelial cells [16,17]. This generates a reduction of pro-inflammatory cytokines, chemokines, and molecules of cellular adhesion and of other enzymes that are involved in the inflammatory response. Specifically, the effects are: a reduction of the recruitment of white blood cells (including monocytes-macrophages but excluding neutrophils) into affected areas, further inhibiting the release of chemotactic signals and the expression of cytokines regulating the function of macrophages, endothelial cells, lymphocyte activities (i.e.: IL-1, IL-2, IL-3, IL-6, TNF- $\alpha$  and granulocyte monocyte-colony stimulating factor (GM-CSF)) and fibroblast proliferation. Further, release of histamine from basophils is impaired.

The non-genomic mechanism is more rapid and is mediated by the interactions with the cytoplasmic GCR or with the membrane GCR [18]. Within a few seconds or minutes after GC binding to GCR, a cascade of effects is activated, including the inhibition of phospholipase A2. This phenomenon is mediated by an increased synthesis of lipocortin-1,



**Fig. 2.** Severity and phases of COVID-19. (A) COVID-19 severity: frequency of degrees of clinical manifestations in a Chinese cohort (> 44.000 patients) (ref: Wu Z. et al., 2020). (B) Phases of COVID-19 disease and timing for the use of glucocorticoids. Legend: **ARDS:** Adult Respiratory Distress Syndrome; **COVID-19:** CoronaVirus Disease-19; **MOF:** multi-organ failure; **pts:** patients; **SIRS:** systemic inflammatory response syndrome.

generating an impaired release of arachidonic acid followed by a decreased production of prostaglandins, leukotrienes and platelet activating factor [16,18].

In addition to the immunosuppressive effects on the proliferation of B and T lymphocytes, as well as the inhibition of monocyte function, high concentrations of GCs reduce complement levels [18,19]. Overall, GC anti-inflammatory and immunosuppressive activity influence the concentration, distribution and function of peripheral leukocytes, with an impairment of the activity of B and T lymphocytes and an increase in the number and activity of neutrophils, whereas in macrophages a reduction of the arachidonic acid metabolites like prostaglandins, leukotrienes and platelet activating factor is observed.

#### 4. Glucocorticoids: treatment of COVID-19

Table 1 summarizes the protocols of GC employed in the treatment of COVID-19 patients.

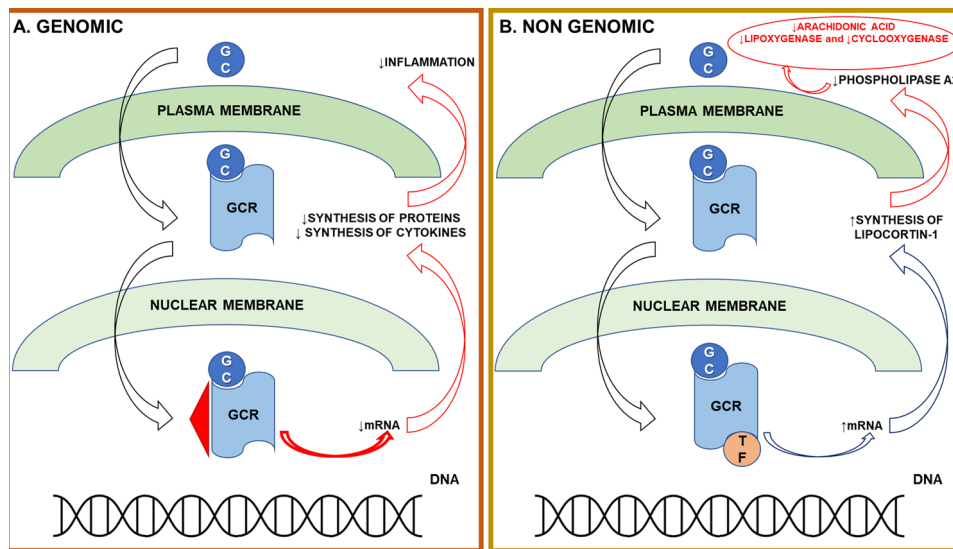
Overall, it was not clear whether patients diagnosed with COVID-19 could take advantage or might be harmed by the use of GCs [15]. At the beginning, WHO did not recommend GCs in this setting<sup>[c]</sup>, considering

the available evidence in the literature, arising from non-randomized studies conducted on patients with MERS that revealed a prolonged viral clearance, without influencing or positively impacting the clinical outcome [12]. Nevertheless, WHO considered it a priority to wait for results from randomized controlled trials (RCT) on the use of GCs, since these drugs might represent complementary treatments potentially useful to save human lives during the COVID-19 pandemic in the future<sup>[d]</sup>. The recently announced results from the RCT on DX will probably change the future scenarios<sup>[b]</sup>.

In some patients affected by SARS-CoV-2-linked pneumonia, the development of an ARDS, potentially responsive to GCs, has been observed. Indeed, a study published in the Journal of American Medical Association has shown favorable data on the use of methylprednisolone (MP), revealing that it might be beneficial in terms of mortality (= mortality reduction: 62 %) [5].

In China MP was employed in hospitalized patients with severe and critically ill stage III, with persistent fever (temperature > 39 °C), with peculiar radiological manifestations in Computerized Tomography scans and with IL-6 levels > 5 ULN (Table 1).

In Italy, the use of GCs was not clearly recommended by the official



**Fig. 3.** Mechanisms of action of synthetic glucocorticoids (GC).

(A) Genomic mechanism. (B) Non-genomic mechanism.

Legend: **GC:** glucocorticoid; **GCR:** glucocorticoid receptor; **mRNA:** messenger RNA; **TF:** transcription factor.

**Table 1**  
Synthetic glucocorticoids (GC) employed in the treatment of patients with COVID-19 in China, Italy, United States (US) and United Kingdom (UK).

Guidelines and therapeutic protocols	GC	Route of administration	Indications for GC use	Dosing	Type of the study
CHINA [n]	MP	IV, OS	<ul style="list-style-type: none"> <li>*For pts:                             <ul style="list-style-type: none"> <li>-in severe and critically ill stage;</li> <li>-with persistent high fever (temperature &gt; 39 °C);</li> <li>-whose computerized tomography (CT) demonstrated patchy ground-glass attenuation or having &gt; 30 % area of the lungs involved;</li> <li>-whose CT demonstrated rapid progression (&gt; 50 % area involved in pulmonary CT images within 48 h);</li> <li>-whose IL-6 is above <math>\geq 5</math> U/LN.</li> </ul> </li> <li>*Appropriate and short-term use of GCs should be considered for pts with severe COVID-19 pneumonia as early as possible.</li> <li>*A high dose of GC should be avoided due to the possible development of adverse events and complications</li> </ul>	<ul style="list-style-type: none"> <li>*Initial MP at a dose of 0.75–1.5 mg/kg IV once a day (nearly 40 mg once or twice a day) is recommended.</li> <li>*MP at a dose of 40 mg q12h can be considered for pts with falling body temperature or for pts with significantly increased cytokines under routine doses of GCs.</li> <li>*MP at a dose of 40 mg–80 mg q12h can be used for critical cases.</li> <li>*The dosage of MP should be halved every 3–5 days if:                             <ul style="list-style-type: none"> <li>-medical conditions of patients are improved;</li> <li>-the body temperature normalizes;</li> <li>-involved lesions on CT are significantly absorbed.</li> </ul> </li> <li>*Oral MP once a day is recommended when the IV dose is reduced to 20 mg per day.</li> <li>*The length of GC treatment is not defined; some experts have suggested ceasing GC treatment when patients are nearly recovered.</li> </ul>	Observational/Retrospective
ITALY Protocols employed by single institutions	MP PD	IV OS	<ul style="list-style-type: none"> <li>Pts in sub-intensive care units till the development of ARDS</li> </ul>	<ul style="list-style-type: none"> <li>*MP: 1 mg/kg/die for 5 days;</li> <li>*Afterwards MP reduction to 0.5 mg/kg/die for further 5 days.</li> <li>*In some protocols PD is used as a latest step (for dose reduction) and is administered per OS.</li> </ul>	Multicentric non randomized controlled cohort trial, in pts with COVID-19 linked ARDS
Study promoted by ASUGI (Azienda Sanitaria Universitaria Giuliano Isontina) [o]	MP	IV, OS	<ul style="list-style-type: none"> <li>Pts hospitalized in Pneumology/UTIR (Respiratory Intensive Care Unit) matching the criteria established by clinical practice</li> </ul>	<ul style="list-style-type: none"> <li>*Day 1: MP: 80 mg IV as bolus, followed by MP: 80 mg in IV continuous infusion in 240 mL of physiological saline solution (0.9%) in 24 h.</li> <li>*The following 8 days: MP: 80 mg in IV continuous infusion in 240 mL of physiological saline solution (0.9%) in 24 h till reachment of P/F &gt; 350 mmHg and/or CRP 2 <math>\leq</math> mg/dL.</li> <li>*When P/F &gt; 350 mmHg and/or CRP <math>\leq</math> 2 mg/dl (or <math>\leq</math> 20 mg/L): oral MP: 16 mg twice a day (or IV MP: 20 mg twice a day) to reduce till withdrawal when CRP is normal (<math>\pm</math> 20 %) and/or P/F &gt; 400 or SatHbO2 <math>\geq</math> 95 % in air.</li> <li>*DX: 20 mg/die for 5 days</li> <li>*Afterwards: 10 mg/die for 5 days</li> </ul>	
SIMIT (Società Italiana di Malattie Infettive e Tropicali) [e] [20]	DX	OS	<ul style="list-style-type: none"> <li>*Pts with slight respiratory symptoms but aged &gt; 70 years and/or with risk factors (COPD, diabetes and cardiopathy);</li> <li>*Symptomatic pts with slight symptoms: fever (temperature &gt; 37.5 °C), cough, slight to moderate dyspnea, and standard thorax X-ray with pneumonitis having BCRSS score (Brescia Covid Respiratory Severity Scale) &gt; 2.</li> <li>*Pts with severe pneumonia, ARDS or global respiratory failure, hemodynamic decompensation: it is necessary to start DX24h after ARDS diagnosis</li> </ul>		
US (Yale University) [i]	MP	IV	<ul style="list-style-type: none"> <li>*May be considered for use by critical care team for salvage therapy.</li> <li>*GC should be used if clinically indicated as part of standard of care such as for an asthma or COPD</li> </ul>	<ul style="list-style-type: none"> <li>*MP: 40 mg q8hr IV for three days, then re-assess</li> </ul>	

(continued on next page)

**Table 1 (continued)**

Guidelines and therapeutic protocols	GC	Route of administration	Indications for GC use	Dosing	Type of the study
UK [p, q]	Low-dose DX [other drugs will be tested: Lopinavir-Ritonavir, Hydroxychloroquine, Azithromycin, Tocilizumab]	IV, OS	exacerbation, or shock with history of chronic steroid use. *Lack of effectiveness and potential harm shown in literature, specifically inhibition of viral clearance in severe influenza and SARS, though possible benefit with critically ill COVID19 patients. *Hospitalized pts diagnosed with SARS-CoV-2 infection	*N.A.	Randomized controlled trial (RECOVERY) EudraCT number: 2020–001113-21
WHO [b] [12,13,25,26]	Do not routinely give systemic GC for treatment of viral pneumonia outside of clinical trials. A systematic review of observational studies of GC administered to patients with SARS reported no survival benefit and possible harms (avascular necrosis, psychosis, diabetes, and delayed viral clearance). Clinicians considering GC use for a patient with COVID-19 and with sepsis must balance the potential small reduction in mortality with the potential downside of prolonged shedding of CoV in the respiratory tract, as has been observed in patients with MERS-CoV. If GCs are prescribed, monitor and treat hyperglycaemia, hypernatraemia and hypokalaemia. WHO has prioritized the evaluation of GCs in clinical trials to assess safety and efficacy.				
[US IDSA (Infectious Diseases Society of America) [27]	Among pts admitted to the hospital with COVID-19 pneumonia, the panel suggests against the use of GC. (Conditional recommendation, very low certainty of evidence). Among pts who have been admitted to the hospital with ARDS due to COVID-19, the panel recommends the use of GC in the context of a clinical trial. (Knowledge gap).				

**Legend:** ARDS: adult respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DX: dexamethasone; GCs: glucocorticoids; h: hours; IV: intravenous; MERS CoV: Middle East Respiratory Syndrome Coronavirus; MP: methylprednisolone; NA: not available; PD: prednisone; P/F: PaO2/FiO2; PO: per os; pts: patients; SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronavirus-2; UK: United Kingdom; US: United States.

guidelines of the principal scientific societies that are involved in the management of COVID-19 patients (i.e., infectious disease<sup>[e]</sup>, anesthesiology<sup>[f]</sup>, pneumology<sup>[g]</sup>, and internal medicine<sup>[h]</sup>). Nevertheless, the use of DX is suggested for the supportive treatment of patients with confirmed ARDS by an online *vademecum* published by the SIMIT (Italian Society of Tropical and Infectious Diseases<sup>[e]</sup>) in the region of Lombardy (the most affected region by COVID-19 in Italy) [20], and also by the recommendations of the Italian National Institute for the Infectious Diseases “L. Spallanzani”, that, as alternative treatment, also suggests the use of MP [21]. Further GCs are used in some Intensive Care Units (ICU), on the basis of the positive results from RCT on patients with severe Community-Acquired Pneumonia (CAP) [22]. Indeed, a number of RCT demonstrated that a prolonged treatment with a moderate dose of GCs, by downregulating the systemic and lung inflammation, is essential for increasing the speed of the resolution of the disease and for restoring tissue homeostasis [23,24].

In United States (US), the use of MP is considered for salvage therapy for the critical care teams, as a part of the standard of care (i.e., for an asthma or chronic obstructive pulmonary disease exacerbation, or shock with history of chronic steroid use<sup>[i]</sup>).

In United Kingdom, GCs were not recommended and a RCT named RECOVERY (EudraCT number: 2020–001113-21<sup>[j]</sup>), is testing a variety of drugs, including single agent low dose DX, whose positive results were recently announced<sup>[b]</sup> (Table 1).

## 5. Ongoing clinical trials

To date > 1300 trials for COVID-19 have been recorded on ClinicalTrials.gov and currently 35 studies explore the use of GCs alone or in association with other drugs for the treatment of patients with SARS-CoV-2 infection (cut-off date: May 10, 2020).

All these studies involving GCs are currently ongoing, with the exception of: 1) a Chinese trial that was permanently suspended because the epidemic of COVID-19 in China (NCT04273321); 2) the NCT04244591 study from Beijing, which started on January 2020 and concluded the final data collection on April 13, 2020) and a 3) recently completed US observational retrospective trial which intends to study the role of early use of MP in the hospitalized patients with a diagnosis of COVID-19 pneumonia (NCT04374071). However, due to the extreme pace and complexity of this disease, no results are yet available from these studies.

Table 2 summarizes the main clinical trials using GCs as single agent therapy for the treatment of COVID-19 in at least one of their treatment arms.

Considering the 27 studies listed in Table 2: 13 trials are currently recruiting, 10 are not yet recruiting, 2 are completed, 1 is suspended, and 1 is enrolling by invitation. Most of these studies are phase II (= 10), followed by 7 phase III, 4 phase IV, 2 phase II/III, 2 observational and 1 phase I/II trials. No classification was provided for one study (NCT04344730). Almost all of the trials cited in Table 2 are randomized except for the 2 aforementioned observational studies (NCT04278404, NCT04374071) and 2 non-randomized trials (NCT04355247, NCT04323592); only 1 study is retrospective (NCT04374071). Monotherapy with GC was tested as an experimental arm in 23 trials while GCs were used as standard control arm in the remaining 4 studies.

The most commonly used GCs are: intravenous (IV) MP, followed by IV DX, IV hydrocortisone and prednisone administered per os. Interestingly, inhaled steroids such as budesonide and ciclesonide are also tested in 4 and 3 trials respectively.

Specifically, IV GCs are being tested mainly in moderate or severe cases of COVID-19 (i.e. young and adult patients requiring non-invasive ventilation, O<sub>2</sub>-dependent disease, subjects needing invasive intubation with mechanical ventilation for moderate/severe ARDS or immediately life-threatening patients admitted to ICU for acute hypoxemic respiratory failure and at high risk for cytokine/chemokine storm

complications), while inhaled steroids are tested in cases of mild disease, mainly for rehabilitation of hyposmia/anosmia that arose immediately after the upper respiratory COVID-19 infection or in patients with moderate symptoms, with the aim to reduce the need for O<sub>2</sub> supplementation.

The remaining studies that have not been included in Table 2 evaluate GCs in association with other drugs as combinational therapies for the treatment of patients with SARS-CoV-2 infection. NCT04371601 is an early phase I randomized trial which explores the addition of umbilical cord mesenchymal stem cells to conventional treatments such as anti-viral, GCs and O<sub>2</sub> therapy versus the above-mentioned symptomatic therapies for patients with severe COVID-19 pneumonia. A French multicenter, randomized phase III trial (NCT04347980) is evaluating DX *plus* hydroxychloroquine in comparison to hydroxychloroquine alone for the treatment of SARS induced by COVID-19.

Intriguingly, the COPERNICO study, a prospective, multicenter, randomized, open-label, phase II trial (NCT04335305), is assessing the efficacy of tocilizumab combined with pembrolizumab compared to standard care with GC, tocilizumab, virally targeted agents, chloroquine or hydroxychloroquine and supplemental O<sub>2</sub> in adult patients with COVID-19 pneumonia and bad prognostic factors who are non-responsive to frontline therapy within 48 h from treatment initiation.

The inhaled steroid budesonide in combination with the  $\beta$ 2 agonist formoterol is under investigation in 2 randomized phase III trials (NCT04331470 and NCT04331054) with the aim to prevent an excessive local immune reaction in the respiratory system.

MP in association with immunosuppressive drugs such as tacrolimus and thalidomide is being tested in a phase III (NCT04341038) and a phase II (NCT04273581) trial, respectively, in patients at high risk for cytokine storm development.

Finally, the REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform Trial for CAP) is an adaptive research platform for the evaluation of multiple treatment modalities in the event of a respiratory pandemic resulting in critical illness, that has set-up a sub-platform called “REMAP – COVID” (NCT02735707) for the evaluation of specific treatments for COVID-19. In particular, the aim of this study is to assess the effect of a range of interventions including hydrocortisone to improve the outcome of patients with SARS-CoV-2 infection admitted to ICU.

## 6. Conclusions

Synthetic GCs represent a well-known, cheap, widely available and easily manageable class of drugs used in a variety of settings, particularly for their immunosuppressive activities. In this review, we have synthesized their principal mechanisms of action and their putative roles in limiting an exaggerated immune response starting in the lung alveoli of 20 % of patients that develop COVID-19.

Despite a previous lack of evidence of a clear benefit for patient survival outcomes, GCs have been used in clinical practice for the management of COVID-19 hospitalized patients, for their hypothetical benefit on respiratory function and consequently their potential effect on reducing the number of patients requiring invasive procedures (i.e., ventilation or intubation). Indeed, in such a health emergency situation, clinicians have employed GCs as an “accepted” therapy, for their reasonable expectation of success in the treatment of individual patients<sup>[k]</sup>. Thus, GCs have been administered according to physician’s judgment, based on the patient’s best interest. To this end, the use of these immunosuppressive drugs has been considered reasonable despite the risk of developing adverse events and that of delaying the clearance of the virus, the resolution of the respiratory failure being the biggest issue in the phases IIb and III of COVID-19 patients. This intervention was reasonable when treating an individual patient, particularly when facing with the lack of effective drugs that had been proven to be effective in this disease at the beginning of the Public Health Emergency. Thus physicians were ethically allowed to use an unproven intervention if

**Table 2**  
Ongoing clinical trials testing GCs in COVID-19.

Trial ID/status	Trial phase	Trial design	Drugs	Dose of GC	Phase of disease	Primary endpoint	Statistical method	Patient population	Ref
NCT04366115 Not yet recruiting	Phase 1	Phase 1: Single-ascending dose Open label	<u>Experimental Arm:</u> AVM0703 plus HCT	Not Provided	Severe cases of COVID-19	<u>Phase 1:</u> ● Safety of AVM0703 ● RP2D  <u>Phase 2:</u> ● Efficacy of AVM0703 + HCT vs HCT alone according to the to the pre-specified outcome measures	<u>Phase 1:</u> Dose-Limiting Toxicity  [Time Frame: 0-12 months]	COVID-19 positive adult pts with immediately life-threatening COVID-19, according to COVID-19 Critical Illness Salvage Criteria	NA
	Phase 2	Phase 2: Randomized Double-blind Placebo-controlled	<u>Standard Arm:</u> Placebo plus HCT		Mild/Moderate cases of COVID-19		<u>Phase 1-2:</u> 28-day all-cause mortality  [Time Frame: 0-12 months]		
NCT04361474 Not yet recruiting	Phase 3	Randomized Single-blind Placebo-controlled Multicenter	<u>Experimental Arm:</u> Nasal irrigation with BUD and physiological saline  <u>Standard Arm:</u> Placebo	BUD 1mg/2mL diluted in 250mL of physiological saline 9'/00	Mild/Moderate cases of COVID-19	Efficacy of BUD vs Placebo according to the pre-specified outcome measures	Percentage of pts with an improvement of more than 2 points on the ODORATEST score (5) after 30 days of treatment  [Time Frame: 30 Days]	Adult pts with a suspected SARS-CoV-2 infection, whether or not confirmed by PCR, or close contact with a PCR-confirmed case, typical chest CT scan or positive serology; with isolated sudden onset hyposmia persisting 30 days after the onset of symptoms of SARS-CoV-2 infection	NA
	Phase 2	Randomized Double-blind Placebo-controlled Single center	<u>Experimental Arm:</u> DX  <u>Standard Arm:</u> Placebo	DX 20 mg IV daily for 5 days followed by 10 mg daily for 5 days	Moderate or Severe cases of COVID-19	Efficacy and Safety of DX vs placebo in mechanically ventilated pts with the hyper-inflammatory sub-phenotype of ARDS due to COVID-19 according to the pre-specified outcome measures	Ventilator Free Days at Day 28  [Time Frame: 28 Days]	COVID-19 positive adult pts with moderate or severe ARDS (P/F ≤ 200mmHg) requiring mechanical ventilation within 7 days prior to randomization  Hyper-inflammatory ARDS Sub-Phenotype	NA
NCT04359511 Not yet recruiting	Phase 3	Randomized Single-blind	<u>Experimental Arm:</u> PD or HCT  <u>Standard Arm:</u> Optimized SoC	PD 0.7 mg/kg/day PO for 10 days, once a day, or HCT 3.5 mg/kg/day IV by continuous infusion for 10 days, if the patient cannot take drugs by oral route	Moderate or Severe cases of COVID-19	Efficacy and Safety of PD or HCT vs SoC according to the WHO Ordinal Scale	Clinical improvement defined by the improvement of 2 points on the WHO 7-category ordinal scale, at 14 days  [Time Frame: 14 days]	COVID-19 positive adult pts with moderate or severe oxygen-dependent disease or with an ARDS with CT scans thoracic images suggestive of diffuse alveolar damage either at the exudative phase or at the pulmonary organization phase	NA
	Phase 4	Randomized Open label	<u>Experimental Arm:</u> BUD  <u>Standard Arm:</u> Optimized SoC	Inhaled BUD	Mild/Moderate cases of COVID-19	Efficacy of Inhaled BUD vs SoC according to the pre-specified outcome measures	Proportion of pts in both arms fulfilling the criteria for treatment failure: ● 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) ● death	COVID-19 positive adult pts hospitalized because of pneumonia status #3 - #4 WHO scale	NA

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Table 2 (continued)

Trial ID/status	Trial phase	Trial design	Drugs	Dose of GC	Phase of disease	Primary endpoint	Statistical method	Patient population	Ref
NCT04355247	Phase 2	Non randomized Open label Pilot study Exploratory trial	<u>Experimental Arm:</u> MP	MP 80 mg IV bolus injection daily x 5 days starting upon day 1 of admission to hospital.	Moderate or Severe cases of COVID-19	Efficacy of MP according to the pre-specified clinical complete or partial response criteria	Clinical complete response criteria [Time Frame: 14 days]  Clinical Partial Response criteria [Time Frame: 14 days]  If < 50% of pts with high risk develop respiratory failure the investigator will consider the treatment as successful	COVID-19 positive adult pts who meet criteria of high risk for severity	NA
NCT04349410	Phase 2 Phase 3	Randomized Open label Multicenter	Following FMTVDM measurements, pts will be randomized into one of the 11 experimental treatment arms including MP  40 to 72 hours later (providing adequate time for treatment effect) FMTVDM will be repeated	MP 80 mg IV over 30-minutes, BID x 7-days. Then taper off	Mild/ Moderate and Severe cases of COVID-19	Efficacy of FMTVDM to investigate the prevalence and severity of Covid-19 pneumonia and to provide rapid determination of treatment response in each pts to direct treatment decisions	Improvement in FMTVDM Measurement with nuclear imaging  [Time Frame: 72 hours]  Measured improvement in tissue as measured using FMTVDM	COVID-19 positive child and adult pts	NA
NCT04348305	Phase 3	Randomized Quadruple-blinded Placebo-controlled Multicenter	<u>Experimental Arm:</u> HCT  <u>Standard Arm:</u> Placebo	Continuous IV infusion of HCT 200 mg over 24 h (total 104 ml). or bolus injection of HCT 50 mg (10 ml) every 6 h if continuous IV infusion is not possible	Severe cases of COVID-19	Efficacy of HCT vs Placebo according to the pre-specified outcome measures	Days alive without life support (i.e. invasive mechanical ventilation, circulatory support or renal replacement therapy) at day 28  [Time Frame: Day 28 after randomization]  A total of 1000 pts will be randomised in order to detect a 15% relative reduction in 28-day mortality combined with a 10% reduction in time on life support among the survivors with a power of 85%	COVID-19 positive adult pts requiring hospitalization and use of one of the following: ● Invasive mechanical ventilation ● Non-invasive ventilation ● Continuous use of CPAP for hypoxia ● O2 supplementation with an independent of delivery system	NA
NCT04345445	Phase 3	Randomized Open label Single center	<u>Experimental Arm:</u> Tocilizumab  <u>Standard Arm:</u> MP	MP 120 mg/day IV over 30 minutes for 3 days	Moderate and Severe cases of COVID-19	Efficacy and Safety of Tocilizumab vs MP according to the pre-specified outcome measures (reducing the need for ventilator support in moderate/severe COVID-19 pts at risk for complications of cytokine storm)	The proportion of pts requiring mechanical ventilation  [Time Frame: Through study completion, and average of 6 months]	Hospitalized symptomatic COVID-19 positive adult pts with the presence of clinical and radiological signs of progressive disease, and laboratory evidence indicative of risk for cytokine storm complications	NA

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Table 2 (continued)

Trial ID/status	Trial phase	Trial design	Drugs	Dose of GC	Phase of disease	Primary endpoint	Statistical method	Patient population	Ref
NCT04344730 Recruiting	NA	Randomized Quadruple-blinded Placebo-controlled Single center	<p><u>Experimental Arm:</u></p> <ul style="list-style-type: none"> <li>Standard O2 and DX</li> <li>CPAP and placebo</li> <li>DX and CPAP</li> </ul> <p><u>Standard Arm:</u></p> <ul style="list-style-type: none"> <li>Standard O2 and placebo</li> </ul>	DX 20 mg/ 5 ml solution for injection in ampoule of 5mL from day 1 to day 10.	Severe cases of COVID-19	Efficacy of DX and O2 support strategies vs placebo according to the pre-specified outcome measures	<p>Mean days of ventilation</p> <p>[Time Frame: Through study completion, and average of 6 months]</p> <p>The time-to-death from all causes</p> <p>[Time Frame: day-60]</p> <p>The time to need for mechanical ventilation</p> <p>[Time Frame: day-28.]</p> <p>In non-mechanically ventilated pts, a 2x2 factorial design will be used to assess the two interventions, separately</p>	ICU COVID-19 positive adult pts with acute hypoxemic respiratory failure	NA
NCT04344288 Recruiting	Phase 2	Randomized Open label Multicenter	<p><u>Experimental Arm:</u></p> <ul style="list-style-type: none"> <li>PD</li> </ul> <p><u>Standard Arm:</u></p> <ul style="list-style-type: none"> <li>Optimized SoC</li> </ul>	PD 0.75 mg/kg/day PO for 5 days, then 20 mg/day for 5 more days	Severe cases of COVID-19	Efficacy of PD vs SoC according to the pre-specified outcome measures	<p>Number of pts with a SpO2 &lt; 90% stabilized at rest and under not more than 5 L / min of supplemental O2 using medium concentration mask</p> <p>[Time Frame: 7 days]</p>	Hospitalized symptomatic COVID-19 positive adult pts with a theoretical respiratory indication for transfer to ICU	NA
NCT04343729 Recruiting	Phase 2	Randomized Quadruple-blinded Placebo-controlled Single center	<p><u>Experimental Arm:</u></p> <ul style="list-style-type: none"> <li>MP</li> <li>Standard Arm:</li> <li>Placebo</li> </ul>	MP 0.5 mg/kg IV BID for 5 days.	Severe cases of COVID-19	Efficacy and Safety of MP vs Placebo according to the Mortality Rate	<p>Mortality rate at day 28</p> <p>[Time Frame: on day 28, after randomization]</p>	COVID-19 positive adult pts with respiratory symptoms suggestive of SARS (cough OR dyspnea) at the time of screening, or diagnosis of SARS, taking into account the following: <ul style="list-style-type: none"> <li>respiratory rate &gt; 24 breaths per minute or reported feeling of shortness of breath;</li> <li>satO2 ≤ 94% in room air</li> <li>use supplementary O2</li> <li>under invasive mechanical ventilation</li> </ul>	NA
NCT04330586 Not yet recruiting	Phase 2	Randomized Open label Multicenter	<p><u>Experimental Arm:</u></p> <ul style="list-style-type: none"> <li>CIC</li> <li>Standard Arm:</li> <li>CIC plus hydroxychloroquine</li> </ul>	CIC 320 ug oral inhalation every 12 h for 14 days	Mild/Moderate cases of COVID-19	Efficacy of CIC alone or in combination with hydroxychloroquine in eradication of SARS-CoV-2 from respiratory tract earlier in pts with mild COVID-19	<p>Rate of SARS-CoV-2 eradication at day 14 from study enrollment</p> <p>[Time Frame: Hospital day 14]</p>	COVID-19 positive adult pts with mild COVID-19 according to the NEWS scoring system 0-4	NA
	Phase 2		<p><u>Experimental Arm:</u></p> <ul style="list-style-type: none"> <li>Siltuximab</li> </ul>		Mild/Moderate	Proportion of pts requiring ICU admission at any time within the			NA

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Table 2 (continued)

Trial ID/status	Trial phase	Trial design	Drugs	Dose of GC	Phase of disease	Primary endpoint	Statistical method	Patient population	Ref
NCT04329650 Recruiting		Randomized Open label Multicenter	<u>Standard Arm:</u> MP	MP 250 mg/24 h IV for 3 days followed by 30 mg/24 h for 3 days	and Severe cases of COVID-19	Efficacy and Safety of Siltuximab vs MP according to the pre-specified outcome measures	study period. [Time Frame: 29 days]	Hospitalized COVID-19 positive adult pts with at least one of the following requirements: <ul style="list-style-type: none"> <li>• Non-critical pts with pneumonia in radiological progression</li> <li>• pts with progressive respiratory failure at the last 24–48 hours</li> </ul>	
NCT04327401 Recruiting	Phase 3	Randomized Open label Multicenter	<u>Experimental Arm:</u> DX <u>Standard Arm:</u> Optimized SoC	DX 20 mg IV daily for 5 days, followed by 10 mg IV daily for 5 days	Moderate and Severe cases of COVID-19	Efficacy and Safety of DX vs SoC according to the pre-specified outcome measures (Ventilator-free days)	Ventilator-free days [Time Frame: 28 days after randomization]	Probable or confirmed COVID-19 adult pts with <ul style="list-style-type: none"> <li>• moderate/severe ARDS defined by the Berlin criteria (P/F ≤ 200mmHg with PEEP ≥ 5cmH2O)</li> <li>• Development of moderate/severe ARDS in less than 24 h before randomization</li> </ul>	NA
NCT04325061 Recruiting	Phase 4	Randomized Open label Multicenter	<u>Experimental Arm:</u> DX <u>Standard Arm:</u> Optimized SoC	DX 20 mg IV daily for 5 days, followed by 10 mg IV daily for 5 days	Severe cases of COVID-19	Efficacy of DX vs SoC according to the pre-specified outcome measures (60-day mortality rate)	60-day mortality [Time Frame: 60 days]	Intubated and mechanically ventilated COVID-19 adult pts <ul style="list-style-type: none"> <li>• with acute onset of ARDS, as defined by Berlin criteria as moderate-to-severe ARDS = 3 which includes:  <ul style="list-style-type: none"> <li>• having pneumonia or worsening respiratory symptoms,</li> <li>• bilateral pulmonary infiltrates on chest imaging (x-ray or CT scan),</li> <li>• absence of left atrial hypertension, pulmonary capillary wedge pressure &lt; 18 mmHg, or no clinical signs of left heart failure</li> </ul> </li> <li>• hypoxemia, as defined by a P/F of ≤ 200 mmHg on PEEP of ≥ 5 cmH2O, regardless of FIO2</li> </ul>	NA
NCT04323592 Recruiting	Phase 2	Non Randomized Open label Single center	<u>Experimental Arm:</u> MP <u>Standard Arm:</u> "historical" but concurrent pts never treated with GC	MP 80 mg IV bolus at admission followed by 80 mg in 240 ml 0.9% saline administered IV at 10 mL/h speed for at least 7 day or more	Severe cases of COVID-19	Efficacy of MP vs SoC according to the pre-specified outcome measures	Composite primary endpoint <ul style="list-style-type: none"> <li>• Death</li> <li>• ICU admission</li> <li>• Invasive mechanical ventilation (yes/not, at least one of three of the composite endpoint)</li> </ul> [Time Frame: 28 days] Comparison of two groups of	COVID-19 positive young and adult pts with the following requirements: <ul style="list-style-type: none"> <li>• P/F &lt; 250 mmHg</li> <li>• Bilateral pneumonia (infiltrates/interstitial)</li> <li>• CRP &gt; 10mg/dL (or &gt; 100mg/L)</li> </ul>	NA

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Table 2 (continued)

Trial ID/status	Trial phase	Trial design	Drugs	Dose of GC	Phase of disease	Primary endpoint	Statistical method	Patient population	Ref
NCT04278404 Recruiting	Observational	Prospective Multicenter	The POP02 study is collecting bodily fluid samples of children prescribed some drugs of interest per SoC, including the following GC:  BUD DX HCT	Not Provided	Mild/ Moderate and Severe cases of COVID-19	PK/PD and Safety Profile of under-studied drugs administered to children per SoC	SARS-CoV-2 positive pts:  (i) Consecutively treated with low prolonged doses of MP (ii) Historical pts never treated with GC  The two groups will be matched (1:1) according to the following criteria: <ul style="list-style-type: none"> <li>• sex</li> <li>• age &lt; 10 years difference</li> <li>• CRP level at admission (difference &lt; 20%)</li> <li>• SOFA score (difference &lt; 20%)</li> <li>• P/F difference &lt; 20%</li> </ul>	<ul style="list-style-type: none"> <li>• a diagnosis of ARDS according to the Berlin definition (JAMA 2012)</li> </ul>	NA
NCT04273321 Suspended	NA	Randomized Open label Multicenter	Experimental Arm: MP Standard Arm: Optimized SoC	MP 1mg/kg/day IV or GTT for 7 days	Mild/ Moderate cases of COVID-19	Efficacy of MP vs SoC according to the pre-specified outcome measures	Incidence of treatment failure in 14 days: <ul style="list-style-type: none"> <li>• The clinical symptoms and signs continue to deteriorate,</li> </ul>	COVID-19 positive adult pts admitted in the general wards for mild/moderate symptoms	NA

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Table 2 (continued)

Trial ID/status	Trial phase	Trial design	Drugs	Dose of GC	Phase of disease	Primary endpoint	Statistical method	Patient population	Ref
NCT04263402 Recruiting	Phase 4	Randomized Single-blind Single center	Experimental Arm (A): MP Experimental Arm (B): MP	Arm (A): MP (< 40 mg/d IV for 7 days) Arm (B): MP (40 ~ 80 mg/d IV for 7 days)	Moderate and Severe cases of COVID-19	Efficacy of different doses of MP compared to each other according to the pre-specified outcome measures	Rate of disease remission ● For moderate pts: disease remission refers to relieved symptoms with improved lung CT; ● For severe pts: disease remission refers to relieved symptoms with improved lung CT; or SPO2 > 93% or P/F > 300mmHg. [Time Frame: day 7]	COVID-19 positive adult pts with any of the following requirements: ● Shortness of breath, RR ≥ 30 bpm; ● In a resting state: SPO2 ≤ 93%; ● P/F ≤ 300mmHg. ● Lung CT conformed to the manifestation of viral pneumonia.	NA
NCT04244591 Completed	Phase 2 Phase 3	Randomized Open label Multicenter	Experimental Arm: MP Standard Arm: Optimized SoC	MP 40 mg IV every 12 h for 5 days	Severe cases of COVID-19	Efficacy and Safety of MP vs SoC according to the pre-specified outcome measures	Lower Murray lung injury score The Murray scoring system range from 0 to 16 according to the severity of the condition. [Time Frame: 7 days after randomization]	COVID-19 positive adult pts with the following requirements: ● Symptoms developed more than 7 days ● P/F < 200 mmHg ● Positive pressure ventilation (non-invasive or invasive) or HFNC higher than 45 L/min for less than 48 h Requiring ICU admission	NA
NCT03852537 Recruiting	Phase 2	Randomized Double-blind Single center	Experimental Arm: MP Standard Arm: Optimized SoC	MP will be administered based on CRP-guided protocol outlined under 'Biomarker-adjusted steroid dosing': ● if CRP < 50 mmol/L: discontinue GC; ● if CRP is between 51-100 mmol/L: 0.5 mg MP ● if CRP is between 101-150 mmol/L: 0.75 mg/kg MP ● if CRP level is between 151-200 mmol/L: 1 mg/kg MP ● if CRP level > 200 mmol/L: 1.5 mg/kg MP	Severe cases of COVID-19	Feasibility of the timely initiation of GC and implementation of biomarker-titrated GC dosing	Percentage of eligible pts adhered to the timely initiation (within 12 h of emergency room admission) and daily GC treatment according to ESCM/SCCM clinical practice guideline (control group) or biomarker concordance (intervention group) [Time Frame: Within 30 days of enrollment in study]	COVID-19 positive adult pts with the following requirements: ● pts admitted to hospital ● Acute respiratory failure (SaO2/FiO2 < 315 or P/F < 300).	NA

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Table 2 (continued)

Trial ID/status	Trial phase	Trial design	Drugs	Dose of GC	Phase of disease	Primary endpoint	Statistical method	Patient population	Ref
NCT04377711 Not yet recruiting	Phase 3	Randomized Double-blind Placebo-controlled Multicenter	<u>Experimental Arm:</u> CIC <u>Standard Arm:</u> Placebo	CIC 160 µg Inhaled	Mild/ Moderate cases of COVID-19	Efficacy and Safety of CIC vs Placebo according to the pre-specified outcome measures	Percentage of pts with subsequent emergency department visit or hospital admission for reasons attributable to COVID 19 by day 30  [Time Frame: Day 30]	COVID-19 positive child, young and adult pts not currently hospitalized or under immediate consideration for hospitalization at the time of enrollment	NA
NCT04381364 Not yet recruiting	Phase 2	Randomized Open label Multicenter	<u>Experimental Arm:</u> CIC <u>Standard Arm:</u> Optimized SoC	CIC 320 µg twice daily for 14 days	Mild/ Moderate cases of COVID-19	Efficacy of CIC vs SoC according to the pre-specified outcome measures	Duration of received supplemental O2 therapy  Time (in days) of received supplemental O2 therapy (defined as being alive and discharged from hospital to home or at least 48 h of not receiving O2 therapy during hospitalization).  [Time Frame: 30 days after study inclusion]	COVID-19 positive adult pts that are hospitalized and require O2 therapy	NA
NCT04377503 Not yet recruiting	Phase 2	Randomized Open label Single center	<u>Experimental Arm:</u> Tocilizumab <u>Standard Arm:</u> MP	MP 1.5 mg/kg/day IV divided into 2 daily doses for 7 days, followed by MP 1 mg/kg/day IV for another 7 days. Finally, MP 0.5 mg/kg/day IV until 21 days of use	Mild/ Moderate and Severe cases of COVID-19	Efficacy and Safety of Tocilizumab vs MP in preventing the cytokine release syndrome	Pts clinical status 15 days after randomization  A seven-category ordinal scale consisting of: 1) Death; 2) Hospitalized on invasive mechanical ventilation or ECMO; 3) Hospitalized on non-invasive ventilation or high flow O2 devices; 4) Hospitalized, requiring supplemental O2; 5) Hospitalized, not requiring supplemental O2 - requiring ongoing medical care (COVID-19 related or otherwise); 6) Hospitalized, not requiring supplemental O2 - no longer requires ongoing medical care; 7) Not hospitalized, limitation on activities and/or requiring home O2; 8) Not hospitalized, no limitations on activities.  [Time Frame: 15 days after randomization]	COVID-19 positive adult pts	NA

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Table 2 (continued)

Trial ID/status	Trial phase	Trial design	Drugs	Dose of GC	Phase of disease	Primary endpoint	Statistical method	Patient population	Ref
NCT04374071 Completed	Observational	Retrospective Multicenter	<u>Experimental Arm:</u> MP  <u>Control group:</u> Optimized SoC without use of GC	MP 0.5 to 1 mg/kg/day IV in 2 divided doses for 3 days	Moderate and Severe cases of COVID-19	Efficacy and Safety of MP vs Pre-GC protocol according to the pre-specified outcome measures	Number of pts transferred to ICU in each group [Time Frame: 14 days follow-up for every pt in each group]  Number of pts needed mechanical ventilation in each group  [Time Frame: 14 days follow-up for every pt in each group]  Number of pts who died in each group  [Time Frame: 14 days follow-up for every pt in each group]	COVID-19 positive adult pts with O2 requirement by nasal cannula, HFNC or mechanical ventilation	NA
NCT04374474 Not yet recruiting	Phase 4	Randomized Open label Single center	<u>Experimental Arm:</u> BUD  <u>Standard Arm:</u> Optimized SoC for olfactory retraining	BUD twice a day	Mild cases of COVID-19	Efficacy of BUD vs SoC in anosmia rehabilitation for post-COVID-19 pts according to the pre-specified outcome measures	Change from S&ST Test at 3 and 6 months [Time Frame: 3and 6 months]  Change from baseline SIT at 3 and 6 months  [Time Frame: 3and 6 months]	COVID-19 positive adult pts with hyposmia/anosmia of onset immediately after an upper respiratory viral illness confirmed on S&ST testing	NA

Legend:

ARDS: adult respiratory distress syndrome; AUC: Area under the curve; BID: Bis in die; BUD: Budesonide; CIC: Ciclesonide; CL/F: apparent oral clearance; Cmax: Maximum concentration; COVID-19: Coronavirus disease 2019; CPAP: Continuous positive airway pressure; CRP: C-Reactive Protein; CT: Computed Tomography; DX: dexamethasone; ECMO: Extracorporeal Membrane Oxygenation; ESICM/SCCM: European Society of Intensive Care Medicine alongside the Society of Critical Care Medicine; FMTVDM: Fleming Method for Tissue and Vascular Differentiation and Metabolism; GC: glucocorticoids; GTT: guttae; h: hours; HCT: Hydrocortisone; HFNC: High Flow Nasal Cannula; ICU: Intensive Care Unit; IL: Interleukin; IV: intravenous; MP: methylprednisolone; NA: not available; NEWS: National Early Warning Score; O2: Oxygen; PCR: Polymerase Chain Reaction; PD: prednisone; PEEP: Positive end-expiratory pressure; P/F: PaO2/FiO2 ratio; PK/PD: Pharmacokinetics and Pharmacodynamics; PO: per os; pts: patients; RP2D: Recommended Phase 2 Dose; RR: Respiratory Rate; SARS-CoV-2: Severe Acute Respiratory Syndrome-Coronavirus-2; S&ST: Snap and Sniff Threshold Test; SoC: Standard of Care; SOFA: Sequential Organ Failure Assessment; SIT: Smell Identification Test; Tmax: Time to achieve maximum concentration; V: Volume of distribution; V/F: apparent oral volume of distribution; WHO: World Health Organization.

they judged it helpful for saving lives, re-establishing health and alleviating suffering (Declaration of Helsinki<sup>[1]</sup>). However, this approach does not apply to the main purpose of research, which requires testing a hypothesis, giving rise to new generalizable knowledge<sup>[k]</sup>. A step forward would be represented by the publication of the results of the RECOVERY RCT<sup>[b]</sup>, revealing a death risk reduction for patients on ventilators and on O<sub>2</sub> therapy treated with low dose DX.

Further, considering that in most of the institutions, GCs have been given in association with other complementary compounds, such as anti-viral, anti-malarial and anti-rheumatic agents, serine protease inhibitors, IL blockers, and LMWH, it is difficult to evaluate whether the benefits for patients are associated with single versus the combination of all these drugs.

In a situation of Public Health Emergency with such a severe life-threatening infection, it had been very hard to plan and wait for results from RCT (i.e., will it be ethically correct to exclude patients from GC treatment?), rendering it a priority to employ drugs that support the vital functions of sick people rapidly. Other issues related to starting clinical trials in this context we acknowledge: 1) the choice of the treatment (old and manageable drugs with well known safety profiles are preferably used with respect to new treatments; but will these old drugs will be administered at the same doses? Or at different doses and treatment schedules?); 2) the selection of patients (at which stage of the disease? In seriously ill versus those with low/mild symptoms? Will seriously ill patients be able to provide an informed consent? Will relatives be allowed to do that, also considering the rules of prevention of the spread of this infection?); 3) clinical trial design: the ideal setting would be double blinded RCT, but is there time to produce an adequate *placebo* for the standard treatment arm? Will the design of the trial be feasible once the number of cases will diminish during the course of the epidemic<sup>[1]</sup>?

Moving to clinical practice, hopefully in the near future, when the incidence and prevalence of the disease decreases, the diagnosis of SARS-CoV-2 infection would be performed at earlier stages, the expertise in the management of the disease will be increased, observations from retrospective analyses and results from clinical trials will be much more numerous, researchers will have clearer ideas on which topics and questions still need to be more clearly addressed.

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## Declaration of Competing Interest

NP reports personal fees from SHIONOGI Ltd, personal fees from MSD, personal fees from Becton & Dickinson, personal fees from Pfizer, personal fees from Cepheid, outside the submitted work.

All other authors (CS, LP, MA, and EM) have no conflict of interest to declare.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.cytogfr.2020.06.012>.

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