Dexamethasone in the Treatment of COVID-19: Primus Inter Pares?

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Abstract: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread globally, becoming a huge public health challenge. Even though the vast majority of patients are asymptomatic, some patients present with pneumonia, acute respiratory distress syndrome (ARDS), septic shock, and death. It has been shown in several studies that the severity and clinical outcomes are related to dysregulated antiviral immunity and enhanced and persistent systemic inflammation. Corticosteroids have been used for the treatment of COVID-19 patients, as they are reported to elicit benefits by reducing lung inflammation and inflammation-induced lung injury. Dexamethasone has gained a major role in the therapeutic algorithm of patients with COVID-19 pneumonia requiring supplemental oxygen or on mechanical ventilation. Its wide anti-inflammatory action seems to form the basis for its beneficial action, taming the overwhelming “cytokine storm”. Amid a plethora of scientific research on therapeutic options for COVID-19, there are still unanswered questions about the right timing, right dosing, and right duration of the corticosteroid treatment. The aim of this review article was to summarize the data on the dexamethasone treatment in COVID-19 and outline the clinical considerations of corticosteroid therapy in these patients.

Keywords: dexamethasone; corticosteroids; COVID-19

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has rapidly spread around the world since its first appearance in China [1–3]. Although the vast majority of patients present with mild symptoms, about 15% of COVID-19 cases become severe [4], with approximately 31–41.8% of hospitalized patients rapidly developing acute respiratory distress syndrome (ARDS) [1,2] with a subsequent increased risk of death. The mortality rates referring to critically ill COVID-19 patients range between 26% and 61.5% around the world [1–4].

Several studies have documented that the severity and clinical outcomes are related to dysregulated antiviral immunity and enhanced and persistent systemic inflammation [5–9], as highlighted by a decreased expression of interferons I/III and hyperinflammatory responses involving the release of proinflammatory cytokines (e.g., IL-6, IL-1, TNF, IL-8, and MCP-1) that are sustaining in time (cytokine storm). Consequently, antiviral and anti-inflammatory therapies have been implemented in the pursuit of timely and effective therapies. As yet, though, no specific pharmacological treatments have been proven efficacious for the treatment of COVID-19 [10].

In the context of inflammation being a key role player in the evolution of severe disease, corticosteroids have been used for the treatment of COVID-19 patients, as they are reported to elicit benefits by reducing lung inflammation and inflammation-induced...
lung injury. Early enough, in the first pandemic wave, corticosteroids were introduced in the treatment of critically ill COVID-19 patients with respiratory failure in low-to-moderate doses and for short courses [4,11–13]. Wu et al. showed that the corticosteroid treatment in patients with ARDS reduced the mortality risk (46% in patients receiving corticosteroids vs. 61.8% in patients not receiving corticosteroids [14]. Furthermore, the Surviving Sepsis Campaign suggests the use of low-dose corticosteroid therapy in COVID-19 patients with refractory shock to suppress the cytokine storm caused by SARS-CoV-2 and to improve peripheral vasodilation [15]. With the RECOVERY trial, a significant benefit of glucocorticoid dexamethasone was shown in patients with COVID-19 on mechanical ventilation or oxygen alone at the time of randomization [16]. Based on the positive results of the RECOVERY trial, the National Institutes of Health (NIH) COVID-19 Treatment Guidelines and the World Health Organization (WHO) approved the findings on the beneficial use of dexamethasone in treating critically ill patients with COVID-19 and recommended the dexamethasone treatment in hospitalized patients with respiratory failure requiring a noninvasive/high-flow oxygen device or invasive ventilation [17]. Nonetheless, several studies have reported deleterious effects caused by the corticosteroid treatment that was associated with the use of an increased dose of corticosteroids [18–20], the delay of SARS-CoV-2 viral clearance in patients receiving corticosteroids [18,21], and the increased risk of secondary infections and complications due to the corticosteroid treatment. Therefore, the clinical benefit of this treatment in COVID-19 patients still remains controversial.

2. Current Evidence

Beyond doubt, the RECOVERY trial showed a clear benefit of dexamethasone in critically ill patients with COVID-19 on mechanical ventilation at the time of randomization as compared to the usual care (28-day mortality of 29.3% vs. 41.4%). Similarly, patients on oxygen alone in the dexamethasone group, when compared to the usual care group, had a lower risk of progression to invasive mechanical ventilation (risk ratio, 0.79; 95% CI, 0.64 to 0.97), a shorter duration of hospitalization (median, 12 days vs. 13 days), and a greater probability of being alive at discharge within 28 days (rate ratio, 1.10; 95% CI, 1.03 to 1.17). No benefit was shown in patients with a milder disease without respiratory failure (28-day mortality of 17.8% vs. 14%) [16].

Two more observational trials of corticosteroids for COVID-19 [14,22] and four review and meta-analysis studies [23–26] showed evidence of benefits in mortality. Of note, Pasin et al. in their metaanalysis [24] of the five basic studies on corticosteroids in COVID-19 [16,27–30] coincided with the RECOVERY trial results in that the survival benefits of corticosteroids exist for mechanically ventilated patients and not for patients with no oxygen need. In line with these positive results, subgroups of COVID-19 patients with ARDS [31,32], increased inflammatory markers [33], or over 60 years of age [30] had the highest benefits from corticosteroids. Improved clinical symptoms, radiological findings, and the respiratory failure of patients with COVID-19 were also reported [34,35]. In a small randomized controlled trial, improved clinical outcomes were reported in patients with COVID-19 receiving a short course of methylprednisolone [13]. Wang et al. [35] also found that the use of methylprednisolone (1 to 2 mg/kg/day for 5–7 days) in twenty-six severe COVID-19 patients was associated with a reduced length of hospitalization and ICU stay.

Collectively, a prospective meta-analysis of the trials by the WHO, with a total of 1703 patients (59% from the RECOVERY trial), confirmed a reduction in the 28-day mortality (summary odds ratio (OR) 0.66, 95% CI 0.53–0.82; p < 0.001) [23].

Nevertheless, the mortality benefits of corticosteroids were not confirmed in a series of other studies [27,28,30,36–39]. The retrospective cohorts of COVID-19 patients, mostly from the first wave in China [18,19,40,41], reported an increased mortality in severely ill patients taking high-dose corticosteroids. Lu, X. et al. [19] mentioned that a 10-mg increase in hydrocortisone resulted in a 4% increase in the risk of death. In accordance were the results
of one meta-analysis study [20] based on low-quality evidence with a high variability. Tables 1–4 summarizes the trials on corticosteroid treatments in COVID-19 patients.

These results should be interpreted with caution owing to the potential bias and confounding factors, since they mostly derive from small-sized single-center observational studies; they include patients of different disease stages or severities, and furthermore, they refer to corticosteroid treatments other than dexamethasone. It is noteworthy that dexamethasone showed favorable results in the RECOVERY trial, especially in the critically ill patients, setting a novel positive view on corticosteroid use in respiratory viral infections in these patients. Hence, understanding dexamethasone’s mode of action merits the uppermost importance.
Table 1. Trials using methylprednisolone (MP); by design (R = randomized in blue and Rs = retrospective and obs = observational in yellow), timing, duration, outcomes (focusing on mortality data), and viral shedding.

| Trial Name/Authors (Reference) | Steroid Used, Dosing | Trial Design, Population | Initiation Timing (Days) | Duration of Administration (Days) | Main Outcome(s) | Secondary Outcome(s) | Viral Clearance |
|--------------------------------|----------------------|--------------------------|--------------------------|----------------------------------|----------------|----------------------|----------------|
| Jeronimo CMP et al. MetCOVID [30] | MP 0.5 mg/kg × 2 vs. placebo | MC/R/DB phase II-b placebo-controlled | NA | 5 | No difference in D28 mortality MP pts > 60 yo had lower D28 mortality | No difference in: D7, D14 mortality / D7 intubation and PFR < 100/LOHS/Radiological presence of fibrosis/BOOP after D7 | No difference on D7 viral clearance |
| Corral-Gudino L et al. GLUCOCOVID trial [13] | MP 40 mg bid × 3 d, then 20 mg bid × 3 d | MC/O-L/R pts on O2 SOC vs. SOC + MP | NA | 6 | Composite endpoint: death, ICU admission, need for NIV MP: no significant effect on endpoint (ITT analysis) MP: beneficial effect (PP analysis) | NA | NA |
| Tang X et al. [42] | MP 1 mg/kg/d vs. no MP | Ps/MC/R Single-blind ward pts | 8 (6–16) since Sx onset | 7 | MP vs. no MP: no difference in incidence of clinical deterioration (4.8 vs. 4.8%; OR 1.00 [95% CI, 0.134–7.442]; p = 1.000) | MP vs. no MP: no difference in: D14 clinical cure rate/time to clinical cure/ICU admission/hospitalization duration/in-hospital mortality (all p > 0.05) | MP significantly prolonged SARS-CoV-2 shedding (median, 11 d vs. 8d; HR 1.782 (1.057–3.003); p = 0.030) |
| Gong Y et al. [21] | MP 1 to 2 mg/kg/d halved every 3 d vs. no MP | Rs | 5–10 | No difference in radiologic progression within 20 d | Longer time to negative PCR in MP group (p = 0.03) | | |
| Trial Name/Authors (Reference) | Steroid Used, Dosing | Trial Design, Population | Initiation Timing (Days) | Duration of Administration (Days) | Main Outcome(s) | Secondary Outcome(s) | Viral Clearance |
|-------------------------------|---------------------|--------------------------|--------------------------|----------------------------------|-----------------|----------------------|----------------|
| Wang et al. [35]              | MP 1 to 2 mg/kg/d   | Obs severe COVID-19 pts  | 10 since Sx onset, 2 since admission, 1 since HFNC initiation | 5–7                | MP: faster SpO₂ improvement, less likely to receive MV ($p = 0.05$), faster ↓ CRP; IL-6. No significant difference in: mortality, ↓ LOHS and ICU LOS. | MP: 37% lower risk of death D28 ($p = 0.003$) and less frequent MV ($p = 0.001$) | No difference in mortality between groups |
| Papamanoli A et al. [43]      | MP median 160 mg (120–180)/d | SC/Rs cohort HFNC > 50%, MP vs. no CS | 10 since Sx onset, 2 since admission, 1 since HFNC initiation | Median: 10 incl tapering | MP Mortality 13.9% vs. 23.9% no MP (HR = 0.51 95% CI, 0.27–0.96, $p = 0.044$). | Dosing scheme not associated with mortality. | Mortality in moderate-severe ARDS: MP 26.2% vs. 60% no CS, OR = 0.23 (95% CI, 0.08–1.71) |
| Fernandez-Cruz et al. [32]    | MP 1 mg/kg/d or pulse | SC/Rs MP vs. no MP       | 10 since Sx onset         | NA                              | No difference in viral clearance with CS | No difference in viral clearance time |
| Zha L et al. [44]             | MP 40–80 mg/day     | Obs/MC CS vs. no CS       | within 24 h after admission | 5                               | LOHS and Duration of Sx: no associated with CS | CS: no influence on viral clearance |
| Li Y et al. [45], Shangai cohort | MP 0.75–1 mg/kg/d ÷ 3 d, then 20 mg MP ÷ 3 d vs. (no MP and rescue CS) | MC/Obs/                   | Early (according to LDH and radiographic progression) | ≤7                             | ↓ MV need in early MP ($p = 0.037$) | No difference in viral clearance time |
| Ma Q et al. [38]              | MP 40–80 mg/d vs. no CS | MC/Rs cohort severe and critically ill pts |                            |                                 | No difference: Mortality, LOHS CS group: ↓ Sx duration | No difference in viral clearance time |
| Trial Name/Authors (Reference) | Steroid Used, Dosing | Trial Design, Population | Initiation Timing (Days) | Duration of Administration (Days) | Main Outcome(s) | Secondary Outcome(s) | Viral Clearance |
|--------------------------------|----------------------|--------------------------|--------------------------|----------------------------------|----------------|----------------------|-----------------|
| Salton F et al. [22]           | MP 80 mg loading dose, then 80 mg/day cont infusion | MC/Obs severe COVID-19 MP vs. no MP | Min 8                    |                                   | Composite endpoint: ICU referral/ intubation need / D28 death: significantly ↓ compared with the control group: aHR, 0.41 | MV free d ΔCRP | Not affected |
| Yuan M et al. [46]             | MP max dose 52.5 mg  | Rs nonsevere pts MP vs. no MP | Median 8.3 since Sx onset | Median duration 10.8              | Nonsevere pts on CS: progressed to severe disease, had ↑ LOHS and ↓ duration of fever (not statistically significant difference vs. non-CS pts) | Nonsevere pts on CS: ↑ duration of viral shedding, (not statistically significant difference) |
| Wu C et al. [31]               | MP vs. no MP         | Rs/Obs                   | NA                       | NA                               | MP in ARDS pts: ↓ risk of death (HR, 0.38; 95% CI, 0.20–0.72, p = 0.003) | NA |
Table 2. Trials using dexamethasone (dexa); design (R = randomized in blue and Rs = retrospective and obs = observational in yellow), timing, duration, outcomes (focusing on mortality data), and viral shedding.

| Trial Name/Authors (Reference) | Steroid Used, Dosing | Trial Design, Population | Initiation Timing | Duration of Administration (Days) | Main Outcome(s) | Secondary Outcome(s) | Viral Clearance |
|-------------------------------|----------------------|--------------------------|-------------------|-----------------------------------|----------------|----------------------|------------------|
| Tomazini BM et al., CoDEX trial [27] | dexamethasone 20 mg iv × 5 d, then 10 mg dexamethasone × 5 d or until ICU discharge | moderate to severe ARDS: SOC vs. SOC + dexamethasone | Not mentioned | ≤10 | Dexam group: mean 6.6 ventilator-free d (95% CI, 5.0–8.2) vs. SOC group: 4.0 ventilator-free d (95% CI, 2.9–5.4), (difference, 2.26; 95% CI, 0.2–4.38; *p* = 0.04). D28 no significant difference in: All-cause mortality Clinical status ICU free d MV duration SOFA | NA |
| RECOVERY trial [16] | dexamethasone 6 mg/day pos or iv | Controlled/O-L CS vs. SOC | NA | 10 | Time to discharge Need for MV Need for CRRT | NA |

Table 3. Trials using hydrocortisone (HC); design (R = randomized in blue), timing, duration, outcomes (focusing on mortality data), and viral shedding.

| Trial Name/Authors (Reference) | Steroid Used, Dosing | Trial Design, Population | Initiation Timing | Duration of Administration (Days) | Main Outcome(s) | Secondary Outcome(s) | Viral Clearance |
|-------------------------------|----------------------|--------------------------|-------------------|-----------------------------------|----------------|----------------------|------------------|
| Dequin P-F et al. [28] | hydrocortisone Cont iv: 200 mg × 7 d, then 100 mg × 4 d, then 50 mg × 3 d | critically ill pts | Total max 14 | D21 Tx failure (death, persistent MV, HFNC): No significant difference between CS and placebo (under-powered, stopped early) D21 organ-support free ds: Probability of superiority compared to no CS: 93% in fixed dose HC 80% in shock dose HC | No significant difference in: need for intubation, proning, ECMO, NO |
| Angus DC et al. [29] | hydrocortisone Fixed: 50–100 mg × 4 Shock hydrocortisone: 50 mg × 4 | O-L/R, severe COVID-19 pts, fixed dose HC vs. shock dose HC vs. no HC | Total max 14 | 7 | Mortality rate: 30% fixed dose 26% shock dose 33% no CS | No significant difference in: need for intubation, proning, ECMO, NO |
Table 4. Trials using different corticosteroids (CS); design (Rs = retrospective and obs = observational and As = ambispective in yellow and MA = meta-analysis and SRMA = Systematic Review and Meta-analysis in orange), timing, duration, outcomes (focusing on mortality data), and viral shedding.

| Trial Name/Authors (Reference) | Steroid Used, Dosing | Trial Design, Population | Initiation Timing | Duration of Administration (Days) | Main Outcomes | Secondary Outcome(s) | Viral Clearance |
|-------------------------------|----------------------|--------------------------|-------------------|-----------------------------------|---------------|---------------------|----------------|
| Wu C et al. [14]              | Max dose: 80 mg MP equiv (IQR = 40–80) mg | SC/Rs/Obs | NA | 7 (4–12) | D-60 in-hospital-mortality: Significant ↓ in CS 
(p = 0.0160) | CS not associated with delayed viral clearance |
| Liu J et al. [18]             | Not mentioned        | Rs/Obs CS vs. no CS      |                |                                    |               |                     |                |
| Li Y et al. [36]              | Median 200 mg/d HC equiv (100–320.9) | Rs/MC critically ill pts CS vs. no CS | 9 (5–14) |                                    |               | CS prolonged viral shedding |
| Lu X et al. [19]              | Different CS, 100–800 mg/day HC equiv | SC/Rs, critically ill pts CS vs. no CS | Median 8 (4–12) |                                    |               | NA                  |                |
| Li Q et al. [47]              | 5 pts on pos prednisone (MP equiv dose 20 mg/d) and 50 pts on iv MP 20–40 mg/d | Rs nonsevere pts early LD CS vs. no CS | 1–5 d after hospital admission | 3 (Oral prednisone) 3–5 (iv MP) | CS: ↑ LOS in nonsevere COVID-19 pneumonia: ↑ risk of progression to severe disease; ↑ use of antibiotics, ↑ duration of fever, ↑ LOSH | CS: viral shedding duration only in nonsevere pts (p < 0.05) |
| Ma Y et al. [48]              | MP equiv 56.6 mg median daily dose | Rs/MC, severe and nonsevere COVID-19 pts | 5 median duration |                                    |               |                     |                |
Table 4. Cont.

| Trial Name/Authors (Reference) | Steroid Used, Dosing | Trial Design, Population | Initiation Timing | Duration of Administration (Days) | Main Outcomes | Secondary Outcome(s) | Viral Clearance |
|-------------------------------|----------------------|--------------------------|------------------|----------------------------------|---------------|---------------------|----------------|
| Li S et al. [49]              | Not mentioned        | Not mentioned            | Not mentioned    | Not mentioned                    | NA            | Factors associated with prolonged viral shedding |
|                               |                      |                          |                  |                                  |               | CS: not independent factor of prolonged viral shedding |
| Shi D et al. [50]             | Rs/SC                |                          |                  |                                  |               | Factors associated with prolonged viral shedding |
|                               |                      |                          |                  |                                  |               | CS: not independent factor of prolonged viral shedding |
| Hu Y et al. [37]              | 0.75–1 mg/kg/d MP equiv | Rs CS vs. no CS         | Median time since Sx on set: 7 | 6 (IQR, 4–8) | Assessment of risk factors for long-term (>30 d) positive SARS-CoV-2 and viral shedding |
| Keller MJ et al. [33]         | CS vs. no CS         | Obs incl children        | Within 48 h of admission |                                  |               | CS vs. no CS: no significant difference in time to negative PCR |

HD (80 mg/day; aHR, 0.67 (95% CI, 0.46–0.96) p = 0.031) but not LD CS (40 mg/day; aHR, 0.72 (95% CI, 0.48–1.08), p = 0.11) potentially delayed viral shedding.
Table 4. Cont.

| Trial Name/Authors (Reference) | Steroid Used, Dosing | Trial Design, Population | Initiation Timing | Duration of Administration (Days) | Main Outcomes | Secondary Outcome(s) | Viral Clearance |
|--------------------------------|----------------------|--------------------------|-------------------|----------------------------------|---------------|----------------------|-----------------|
| Wu J et al. [40]               | MP equiv dose 40 mg/d | Rs severe and critically ill pts | 24 h after Dx     | Median 6 (3–10)                  | CS independently associated with ↑ in-hospital mortality in severe COVID-19 (HR = 1.43, 95% CI: 0.82–2.49, \( p = 0.201 \) in IPTW; HR = 1.55, 95% CI: 0.83–2.87, \( p = 0.166 \) in PSM) and critically-ill pts (HR = 3.34, 95% CI: 1.84–6.05, \( p < 0.001 \) in IPTW; HR = 2.90, 95% CI: 1.17–7.16, \( p = 0.021 \) in PSM) | CS: ↓ ICU admission | CS not associated with in-hospital mortality |
| Albani F et al. [39]           | Median dexe equiv dose 20 mg/day | Rs CS vs. no CS | Not mentioned | Median duration: 7/4 in general/severe pts | CS: no significant difference in viral shedding irrespective of severity | CS: ↓ ICU admission |
| Fang X et al. [51]             | Median dose (HC equiv) pos 237.5 mg/iv 250 mg in general/severe pts | Rs, pts of different severity, CS vs. no CS | Not mentioned | Median duration: 7/4 in general/severe pts | CS during hospitalization (aHR, 3.5; 95%CI, 1.8–6.9) was significant risk factor associated with death in severe COVID-19 | NA |
| Li X et al. [41]               | Median cumulative dose equiv to 200 mg prednisone | As, CS vs. no CS | NA | Median duration: 4 | | | |


Table 4. Cont.

| Trial Name/Authors (Reference) | Steroid Used, Dosing | Trial Design, Population | Initiation Timing | Duration of Administration (Days) | Main Outcomes | Secondary Outcome(s) | Viral Clearance |
|--------------------------------|----------------------|--------------------------|-------------------|-----------------------------------|---------------|-----------------------|----------------|
| Sarkar S et al. [20] | SRMA (2 RCTs and 10 cohorts) | | | | CS: ↑ mortality (OR = 1.94, 95%CI: 1.11–3.4, I² = 96%), irrespective of severity or dosage and ↑ LOHS (MD = 1.18 d, 95%CI: −1.28 to 3.64, I² = 93%) | CS may prolong viral shedding (MD = 1.42 d, 95%CI: −0.52 to 3.37, I² = 0%) |
| Sterne JAC et al. REACT [23] | Different CS in different schemes | Ps/MA (7 RCTs) CS vs. SOC | | CS: ↓ all-cause D28-mortality: dexta vs. SOC OR 0.64 [95% CI, 0.5–0.82, p < 0.01], HC vs. SOC OR 0.69 [95% CI, 0.53–0.82, p = 0.13], MP vs. SOC OR 0.91 [0.29–2.87, p = 0.87] | No difference in serious AEs |
| Pasin L et al. [24] | SRMA (5 RCT)CS vs. any other Tx | | | CS: ↓ Mortality rate (26% in CS vs. 28% in no CS, RR = 0.89, CI 95%, 0.82–0.96, p = 0.003) CS: ↑ mortality in pts on no O₂ | Significant ↓ of MV risk in CS group |
| Van Paassen [25] | Diverse CS strategies | SRMA (RCTs and Obs) | | CS are beneficial in short-term mortality | CS: ↓ MV need | CS: not clear effect on viral clearance |
| Trial Name/Authors (Reference) | Steroid Used, Dosing | Trial Design, Population | Initiation Timing | Duration of Administration (Days) | Main Outcomes | Secondary Outcome(s) | Viral Clearance |
|-------------------------------|----------------------|--------------------------|------------------|----------------------------------|---------------|----------------------|----------------|
| Cano EJ et al. [26]           | Different CS in different doses | SRMA                    |                  |                                  | Mortality benefit in CS group in severe COVID-19: OR, 0.65; 95% CI, 0.51–0.83, \( p = 0.0006 \). No benefit or harmful effect among HD and LD CS | LD CS no significant effect on viral shedding |

AE = Adverse Events, aHR = adjusted hazard ratio, ARF = acute respiratory failure, As = ambispective, CI = confidence interval, cont = continuous, CS = corticosteroids, DB = double-blind, dexam = dexamethasone, Dx = diagnosis, equiv = equivalent, HC = hydrocortisone, HD = high-dose, HR = Hazard Ratio, incl = including, IPTW = inverse probability of treatment weighting, IQR = interquartile range, ITT = Intention-to-treat, LD = low-dose, LO(H)S = Length of (hospital) stay, MA = meta-analysis, MC = Multicenter, MP = methylprednisolone, MV = mechanical ventilation, NA = not applicable, NIV = noninvasive ventilation, Obs = observational, O-L = Open-label, OR = odds ratio, pos = per os, PP = per protocol, Ps = prospective, PSM = propensity score matching, pts = patients, R = Randomized, RCT = Randomized-controlled trial, RR = relative risk, Rs = Retrospective, SC = single center, SHR = subhazard ratio, SI = systemic inflammation, SOC = standard of care, Sx = symptom(s), SRMA = Systematic Review and Meta-analysis, Tx = treatment, vs. = versus, yo = years old, and ∆ = change.
3. Dexamethasone in COVID-19: Mode of Action

Corticosteroids are known to temper down the host inflammatory response in the lungs, which may lead to acute lung injury and ARDS [52]. They exert their anti-inflammatory effects by binding to their receptor, the glucocorticoid receptor-GR. GR is a ligand-activated transcription factor whose signaling plays a key role in the modulation of numerous biological functions of the immune cells. Upon ligand binding, GR translocates to the nucleus, where it can enhance transcription by binding to glucocorticoid response elements (GREs). On the other hand, GR, when tethering directly to negative glucocorticoid response elements (nGREs) or GRE half-sites or by binding to transcription factors such as NF-κB, may repress the expression of several genes [53]. Thus, it is evident that the corticosteroid treatment is a double-edged sword, which may induce or inhibit inflammatory cell activity. Several studies have shown that corticosteroids may inhibit T-lymphocyte immunity, an important antiviral mechanism, resulting in persistent viral replication and a delay in viral clearance. At the same time, the suppression of proinflammatory cytokines such as TNF, interleukins, and other genes, such as cyclooxygenase-2 and inducible nitric oxide synthase (iNOS), and the inhibition of the neutrophils, macrophages, and lymphocytes inflammatory activity are documented as effects of corticosteroid use [54].

Dexamethasone has both anti-inflammatory and immunosuppressive effects. Specifically, when binding to GR, it initiates a cascade of immune cell responses that lead to the suppression of proinflammatory cytokines, such as IL-1, IL-6, IL-8, TNF, and IFN-γ, by inhibiting gene transcription [54]. In the case of SARS-CoV-2 infection, those are the produced proinflammatory cytokines that result in local tissue inflammation and in the so-called “cytokine storm” [55]. Furthermore, dexamethasone exerts anti-inflammatory effects by inhibiting macrophage activation [56], neutrophil’s adhesion to endothelial cells, and the release of lysosomal enzymes, preventing chemotaxis at the site of inflammation. Finally, it increases IL-10 gene expression, thus exhibiting further anti-inflammatory effects [57].

Another important function of dexamethasone is its implication in the process of the resolution of inflammation by inducing the D-series pro-resolving lipid mediator pathway via the formation of protectins D1 and DX7 and of 17S-dihydroxydocosahexaenoic acid (17S-HDHA) [58]. These agents have documented roles in driving the resolution of inflammation by regulating the termination of proinflammatory responses, the removal of inflammatory cells, and the tissue repair mechanisms [59]. Finally, certain lipid mediators have been shown to diminish pathologic thrombosis and NETosis, decrease the levels of procoagulant factors and fibrinogen, enhance the removal of clots, and increase the anticoagulant factors [60]. These functions are of high importance, since the thrombotic pathways are central in the pathology of COVID-19 infection.

Overall, in critical COVID-19 patients, glucocorticoid therapy exerts several functions, such as effective homeostatic corrections and consequent improvement in the critical illness-related corticosteroid insufficiency (CIRCI), control of inflammation, and stabilization of cardiovascular and metabolic functions. Furthermore, it induces increased mitochondrial biogenesis, corrects the content and functions of the mitochondria, and decreases the devastating tissue oxidation that leads to multiple tissue and organ dysfunctions [61].

4. Dexamethasone in COVID-19: Clinical Considerations

Starting with the main results of the RECOVERY trial, the most robust until now, that gave dexamethasone a central role in the treatment of COVID-19, dexamethasone at a dose of 6 mg per day for ten days was effective at reducing the mortality rate in both ventilated and oxygenated patients by one-third and one-fifth, respectively, compared to the usual care alone [16].

However, several questions relative to corticosteroid therapy arose:
1. Why use dexamethasone instead of other corticosteroids?
2. When to start corticosteroids?
3. At what dose and for how long?
4. Do they prolong viral shedding?
5. How safe are corticosteroids in the treatment of severely affected COVID-19 patients?
6. What is the role of inhaled corticosteroids in preventing or treating COVID-19 patients?
7. Why use dexamethasone instead of other corticosteroids?

Pharmacologically, dexamethasone has a more advantageous pharmacokinetic/pharmacodynamic (PK/PD) profile. Dexamethasone is a long-acting synthetic corticosteroid with systemic effects and is almost 25 times more potent than other synthetic corticosteroids, as depicted by the equivalent steroid doses (40-mg hydrocortisone:10-mg prednisolone:8-mg methylprednisolone:1.5-mg dexamethasone) [62].

Dexamethasone’s higher potency is explained by its higher affinity for the glucocorticoid receptor compared to other steroids, leading to a more profound genomic and metagenomic activity [62–64] and consequent greater inhibition of the proinflammatory pathways. Additionally, it possesses minimal mineral corticoid activity, limiting the undesired retention of the fluid and sodium. On the PK side, dexamethasone has a longer half-life of 36–72 h, allowing for once-daily dosing [65].

4.1. When to Start Corticosteroids?

The time of corticosteroid treatment initiation is of great importance in order to have favorable outcomes. Siddiqi and Mehra [66] suggested three escalating phases of COVID-19 disease progression, with associated signs, symptoms, and potential phase-specific treatments: the early infection phase, the pulmonary phase, and the hyperinflammation phase, in which anti-inflammatory treatments (such as corticosteroids) are recommended as beneficial. Indeed, in the RECOVERY trial [16], a clear benefit was shown in the patients who were treated with dexamethasone for more than 7 days after symptom onset, when inflammatory lung damage was likely to be more common, and not among those with more recent symptom onsets. It is evident that randomized controlled trials are needed in order to clarify the right timing for the initiation of a corticosteroid treatment course.

4.2. At What Dose and for How Long?

Another consideration is whether “one size fits all” and how effective dexamethasone is in the dose of 6 mg/day for ten days in all COVID-19 patients with respiratory failure, irrespectively of them developing ARDS or not. This daily dose is considered low, with few adverse events [39], as opposed to the 20–40 mg needed daily for hematologic malignancies, autoimmune diseases, or shock.

In an early single-center observational study in Wuhan [61], there was a lower risk of death in the patients who received low-dose corticosteroids (<1 mg/kg/day) or no corticosteroids at all compared to high-dose regimens, but the difference was not statistically significant.

In the CoDEX randomized trial in patients with COVID-19 with moderate-to-severe ARDS, the dose of dexamethasone administered (20 mg of dexamethasone intravenously daily for 5 days and 10 mg of dexamethasone daily for 5 days or until ICU discharge) [27] was higher than that used in the RECOVERY trial. The selection of this higher dose was based on the design of a previous study [67] in patients with non-COVID-19 ARDS who were treated with dexamethasone (or equivalent) in the dose of 30 mg/day. Eventually, a statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) was shown over 28 days, with a good safety profile [27].

Furthermore, Papamanoli et al. [43] showed that, in nonintubated patients with severe COVID-19 pneumonia, higher doses of methylprednisolone (160 mg for a median duration of approximately 10 days) were associated with a lower risk for mechanical ventilation or death (37%) and without consequent adverse effects. Interestingly, among the intubated patients, those that were treated with corticosteroids had more ventilator-free days and shorter length of ICU stays compared to the patients not receiving corticosteroids.

Fernandez-Cruz et al. [32] showed lower in-hospital mortalities in patients with SARS-CoV-2 pneumonia treated with corticosteroids, no matter if they received an initial regimen of 1 mg/kg/day of methylprednisolone or with corticosteroid pulses.
A more recent review and meta-analysis of 35 studies by Cano et al. [26] depicted the high heterogeneity of the practices in dosing steroids; in 74.2% of the studies, steroids were given in low doses, in 11.4%, in high or pulse doses, and in 5.6%, a mixed regimen was used. The meta-analysis failed to prove a beneficial or harmful effect of either dosing scheme.

To complicate the dosing dilemmas further, the published data showed that serum albumin plasma levels, competing drugs, and albumin glycation are important clinical variables influencing the effectiveness of dexamethasone in treating COVID-19 patients [68]. Each one of these factors decreases the binding capacity of albumin, complicating the transport capacity of dexamethasone and resulting in a shorter half-life of the drug and potential toxicity at its peak concentration. It might be appropriate to modify the dose of dexamethasone according to the albumin levels, patient’s weight, and/or plasma levels in order to achieve the therapeutic levels and to avoid toxicity [69].

From a pathophysiology point of view, as Chrousos and Meduri concluded, corticosteroid administration in severe COVID-19 should start early, before the irreversible exhaustion of homeostatic reserves, with large doses to saturate the ubiquitous glucocorticoid receptors, so that the maximum effect is attained [70,71]. Following precision medicine, the dosing of corticosteroids should be tailored to each patients’ unique manifestations, as Gogali et al. explained [72]. From the evidence-based medicine side, though, it is evident that the optimal corticosteroid dosing and duration of treatment still need clarification, especially in critically ill COVID-19 patients with ARDS. Towards this direction, the results of currently undergoing trials like “HIGHLOWDEXA” [20], assessing the efficacy of high doses of dexamethasone (20 mg/day for 5 days and then 10 mg/day for 5 days) vs. low doses of dexamethasone (6 mg/day for 10 days) in patients with respiratory failure might shed more light on the therapeutic algorithms of severe COVID-19.

4.3. Do Corticosteroids Prolong Viral Shedding?

An analysis of the retrospective observational studies from the first pandemic wave showed results associating corticosteroids with immune suppression, an increased viral load, delayed clearance from the body, and increased mortality [21,22]. The early administration of corticosteroids in non-severely ill patients may be deleterious due to an increase in viral shedding or a delay in viral clearance [46]. Prolonged viral shedding has been supported by several retrospective studies [14,36]. Notably, nonsevere COVID-19 pneumonia patients who received early corticosteroid treatment had a more prolonged viral shedding compared to patients of similar severity who did not receive corticosteroids, as was shown in two cohorts [47,48] and one randomized study [42]. A recent review and meta-analysis of 15 studies examining, among others, the SARS-CoV-2 clearance concluded a delay in viral clearance in patients receiving corticosteroids compared with patients who did not receive corticosteroids but failed to prove a statistical significance [20]. Importantly, there are implications that viral shedding prolongation follows a dose-dependent scheme of corticosteroids [49]. However, this theory was not confirmed in the study of Fang et al. [51], who used a low dose of corticosteroids in patients with COVID-19; there was no significant difference in the duration of viral shedding between patients receiving and patients not receiving corticosteroids, irrespective of the severity of the disease. Accordingly, no significant difference in the viral clearance was shown in other studies [22,30,37,38,45]. Two retrospective studies by Xu, K. and Shi, D. [73,74] concluded that corticosteroids were not independent predictors of prolonged viral shedding as opposed to the male sex, lymphocytopenia, APACHE score, and IVIG treatment.

To sum up, there is no clear conclusion as to whether corticosteroids delay the SARS-CoV-2 clearance, and more importantly, there is no certainty about the clinical significance of this.

4.4. How Safe Are Corticosteroids in the Treatment of Severely Affected COVID-19 Patients?

The long-term use of corticosteroids has well-established adverse effects. The short-term use of steroids, although frequent in the pre-pandemic era, was only recently exam-
ined for its potential adverse effects. Two large population-based studies in adults, an American [50] and a Chinese [75] one, underline the increased risk of complications in the outpatient setting. Waljee et al. [50] concluded that, within 30 days of steroid initiation, there was a two to five-fold increase in the incidence rates of fractures, venous thromboembolism, and admission for sepsis, in that order of frequency, in steroid users 18–64 years of age compared to non-users. Yao et al. [75] found a significant increase in gastrointestinal bleeding, sepsis, and heart failure in the respective Chinese population.

Currently the recommendations on corticosteroid use in COVID-19 concern severely ill inpatients requiring O₂ or mechanical ventilation and definitely not outpatients. Is this sicker population threatened by the same harms of short-term corticosteroids use as the general population? The existing literature on COVID-19, although abundant, is not centered on adverse events.

Certain studies concluded that there were no significant differences in serious adverse events between corticosteroid and the standard-of-care groups [24,27,37,42,45,46], while others pointed to a greater probability of myocardial or liver injury, shock [21], and agitation [23] in corticosteroid-treated COVID-19 patients.

Supporting the safety of corticosteroids, the RECOVERY trial [16] reported a similar incidence of new cardiac arrhythmia in the dexamethasone group and the usual care group. In a total of 2104 patients, there were four reports of serious adverse reactions that were deemed by the investigators to be related to dexamethasone: two of hyperglycemia, one of gastrointestinal hemorrhage, and one of psychosis (all recognized adverse effects of corticosteroids).

In the CAPE COVID trial [28], which was stopped early after the publication of the results from the RECOVERY trial, the administration of a low dose hydrocortisone in 148 patients was followed by three serious events: one was cerebral vasculitis, attributed to the SARS-CoV-2 itself, the second was an episode of pulmonary embolism with cardiac arrest, which was considered single and unrelated to steroids, and the third event was an intrabdominal hemorrhage related to anticoagulation for pulmonary embolism.

In REMAP-CAP [29], the only adverse events that were considered relevant to the corticosteroid treatment were one event of neuromyopathy and one event of fungemia.

The recently published results of the OUTCOMEREA network [76] showed that COVID-19 critically ill patients have a higher risk for bloodstream infections (BSI) than their non-COVID-19 counterparts after 7 days of ICU stay, but this negative event was associated with the use of anti-IL-1 and anti-IL-6 and not to corticosteroids. Similarly, no difference in BSI incidence was detected in the MetCOVID randomized trial [30] or the retrospective study by Papamanoli et al. [43].

On the contrary, Giacobbe et al. [77] in their retrospective single-center study, found a higher BSI risk for corticosteroid-treated patients (csHR 3.95, 95% CI 1.2–13.03) than those receiving only tocilizumab (csHR 1.07, 95% CI 0.38–3.04), the risk being even higher with their combination (csHR 10.69, 95% CI 2.71–42.17).

The clinical research points towards an association between corticosteroid use and secondary infections. More secondary infections with sepsis have been recorded [26,36], but the difference was not always significant [13]. The indirect evidence on increased secondary infections may come from the increased antibiotic use in corticosteroid-treated patients, as two retrospective studies [47,48] and one systematic review and meta-analyses [26] have shown.

The literature is more extensive on fungal infections in COVID-19 patients. Corticosteroid treatment is a well-known risk factor for invasive mycoses [78]. An excellent review of retrospective studies from China and Europe reported a 20–35% incidence of COVID-19-associated pulmonary aspergillosis (CAPA) [79] A case report of mucormycosis following the treatment with dexamethasone was reported in a 44-year-old diabetic woman [80] raising concerns about the duration and dosing of the corticosteroid treatment in diabetic COVID-19 patients. Hyperglycemia, which led to increased doses of insulin, was
mentioned in most studies [13,23,30,42] as an adverse event of the corticosteroid treatment as expected, but it was not severe [27].

Reviewing the literature concerning the adverse events of corticosteroid treatment in COVID-19 patients, we underline a significant deficit, as safety is not among the primary outcomes of most studies. This is not a surprise, because corticosteroids are used extensively, and physicians are very familiar with their use. Additionally, some of the main adverse effects of corticosteroids (i.e., VTE, secondary infections and GI hemorrhage) are the main COVID-19 complications or harms from other necessary treatments (i.e., anticoagulation), and perhaps, it is difficult to discriminate the proportional contribution of the virus or the steroids.

Targeting a safe treatment alternative to systemic corticosteroids, inhaled corticosteroids (ICS) have been proposed. There is a cumulative experience of ICS in chronic airways diseases like asthma and COPD, linking their use to changes in the microbiome and, finally, to the increased frequency of upper and lower respiratory tract infections [81,82]. However, an association of ICS with the susceptibility to viral infections is lacking. Instead, a paradoxical protection against viral infections has risen [83,84]. Ciclesonide seems to block SARS-CoV-2 replication in vitro, and in addition, it impedes its cytopathogenicity [85,86]. Early-stage COVID-19 treatment with inhaled corticosteroids might inhibit the progression of SARS-CoV-2 infection to COVID-19. This was shown in a small study of COVID-19 patients on oxygen (not mechanically ventilated) who improved after the treatment with inhaled ciclesonide [87] Similarly, there was in vitro evidence of budesonide’s direct antiviral and anti-inflammatory properties [88]. In the recent open-label, in parallel groups, phase 2 randomized control trial in mild outpatient COVID-19 patients that received inhaled budesonide vs. the usual care, a 91% reduction in the relative risk for COVID-19-related urgent care or hospitalization was shown in the budesonide-treated patients [89].

Patients with chronic lung disease, often on long-term ICS, form a special subcategory of COVID-19 patients. A systematic review of the patients with coronavirus acute respiratory infections (MERS, SARS and COVID-19) by Halpin et al. [90] did not reach a clear-cut conclusion as to whether premorbid use or the continuous administration of ICS is a benefit. Currently, there is a suggestion against the withdrawal of chronically used ICS; asthma and COPD patients receiving ICS are advised to carry on with their treatments [91,92]. Table 5 summarizes the commonest reported adverse events.
Table 5. Trials and corticosteroid (CS)-related adverse effects (randomized trials in blue, retrospective/observational trials in yellow, and meta-analysis in orange).

| Trial Name                  | Steroid Used, Dosing                                                                 | Initiation (Days) | Duration (Days) | Hyperglycemia       | GI               | CNS              | CVS              | Secondary Infections                                                                 | Other |
|-----------------------------|-----------------------------------------------------------------------------------|-------------------|----------------|---------------------|-------------------|------------------|------------------|---------------------------------------------------------------------------------------|-------|
| Jeronimo CMP et al. MetCOVID [30] | MP 0.5 mg/kg bid vs. placebo MP 40 mg bid × 3 d, then 20 mg bid × 3 d            | 5                 | MP group: ↑ insulin                          | MP: ↑ Glu (p = 0.015) | No difference in BC positivity | MP: ↑ Secondary infections (p = 0.637) |                               |                                           |       |
| Corral-Cudino et al., GLUCO-COVID [13] | 1 mg/kg/d MP vs. no MP 160 mg MP (120–180)                                        | Min 7 after Sx onset | 6             | No MP: ↑ Glu (p = 0.313) | Either group: No stress ulcers/GI bleed | Either group: No delirium |                               |                                           |       |
| Tang X et al. [42]          | 1 mg/kg/d MP 80 mg MP loading dose, then 80 mg/day cont infusion                  | Median time 8 (6–16) after Sx onset 10 from Sx onset, 2 from admission, 1 from HFNC initiation | 7             | Either group: No stress ulcers/GI bleed | Either group: No delirium |                               |                                           |                                 |       |
| Papamanoli A et al. [43]    | 160 mg MP (120–180)                                                               | Median: 10 incl tapering | 10            | GI bleed: no difference | MP: Mild agitation more common |                               |                                           |                                 |       |
| Salton F et al. [22]        | MP max dose 52.5 mg, nonsevere pts                                                | Median 8.3 from Sx onset | 10            | GI bleed: no difference | MP: Mild agitation more common |                               |                                           |                                 |       |
| Yuan M et al. [46]          | dexa 6 mg/day pos or iv 20 mg dexa iv × 5 d, then 10 mg dexa × 5 d or until ICU discharge | 1/2104 pts         | 1/2104 pts | Psychosis: 1/2104 |                                                           |                                           |                                 |                                 |       |
| RECOVERY trial [16]         |                                                                              | 2/2104 pts         | 1/2104 pts | Psychosis: 1/2104 |                                                           |                                           |                                 |                                 |       |
| Tomazini BM et al. CoDEX trial [27] | 6 mg/day                          | ≤10                | Insulin need: Dexa: 31.1% vs. SOC 28.3% | Dexa 21.9% vs. SOC 29.1% | Other serious: dexa 3.3% vs. 6.1% SOC |                                           |                                 |                                 |       |
| Trial Name | Steroid Used, Dosing | Initiation (Days) | Duration (Days) | Hyperglycemia | GI | CNS | CVS | Secondary Infections | Other |
|------------|---------------------|------------------|----------------|---------------|----|-----|-----|----------------------|-------|
| Dequin P-F et al. [28] | Cont iv: 200 mg HC × 7d, then 100 mg × 4d, then 50 mg × 3 d | | | | | | | D28: nosocomial infection: 37.3% HC vs. 41.1% placebo (p = 0.42). | HC: 3 serious AE considered unrelated: Cerebral vasculitis, Cardiac arrest 2nd to PE, IA bleed 2nd to anticoagulation |
| Angus DC et al. [29] REMAP-CAP COVID-19 | Fixed HC: 50–100 mg qid vs. Shock HC: 50 mg qid vs. No CS (101 pts) Median 200 mg/d HC equiv | | 7 | | | | 1 episode of fungemia in fixed dose HC | |
| Li Y et al. [36] | Not mentioned | | | | | | 1 episode of neuromyopathy in fixed dose HC | |
| Liu J et al. [18] | 20 mg/d or iv MP 20–40 mg/d | 1–5 after hospital admission | Pos prednisone × 3, iv MP × 3–5 | | | | | |
| Li Q et al. [47] | Pos Prednisone (MP equiv dose median daily dose) | | | | | | | CS in nonsevere COVID-19 pneumonia: ↑ use of antibiotics | |
| Ma Y et al. [48] | CS 56.6 mg (MP equiv) median daily dose | | 5 median duration | | | | CS: ↑ antibiotic use regardless of disease severity (p < 0.001) | |
| Hu Y et al. [37] | 0.75–1 mg/kg/d MP equiv | Median since Sx onset: 7 | 6 (IQR, 4–8) | No difference | | | | |

Liver injury: CS 18.3% vs. 9.9% no CS (p = 0.001)
Myocardial injury: CS 15.6% vs. 10.4% no CS (p = 0.041)
Shock: CS 22% vs. no CS 12.6% (p < 0.001)
| Trial Name                    | Steroid Used, Dosing                                                                 | Initiation (Days) | Duration (Days) | Hyperglycemia | GI          | CNS                        | CVS                          | Secondary Infections          | Other                                                      |
|------------------------------|--------------------------------------------------------------------------------------|-------------------|----------------|--------------|-------------|----------------------------|-------------------------------|-------------------------------|-----------------------------------------------------------|
| Li Y et al. [45]             | MP 0.75–1 mg/kg/d × 3 d, then 20 mg × 3 d vs. (no MP and rescue CS)                  | Early (according to LDH and radiographic progression)         | ≤7             |              |             | No difference in psychosis | No difference in secondary infections | No difference in osteoporosis, avascular necrosis         |
| Buetti N et al. [77]         | Matched case-control study COVID-19 vs. non-COVID-19 ICU pts                          |                   |                |              |             |                            |                               | COVID-19 pts:↑ BSI probability, esp after 7 d of ICU admission compared to non-COVID-19 ICU pts (< 0.00001). COVID-19 pts: significantly ↑ ICU-BSI risk if received anti-IL-1 or anti-IL-6 (sHR 3.20, 95% CI 1.31–7.81, p = 0.011) but not in pts who received CS. |
| Sterne JAC et al. REACT [23] | Different CS in different schemes                                                    |                   |                |              |             |                            |                               | No difference in serious AEs                                  |
| Van Paassen [25]            | Diverse CS strategies                                                                |                   | 5–10           |              |             |                            | CS: ↑ use of antibiotics and ↑ secondary infections or sepsis | No difference in serious AEs                                  |

BC = blood culture, BSI = bloodstream infections, esp = especially, GI = gastrointestinal, ↑ Glu = hyperglycemia, IA = intra-abdominal, PE = pulmonary embolism, and VAP = ventilator-associated pneumonia.
CNS=central nervous system; CVS: cardiovascular system.
5. Conclusions

In conclusion, dexamethasone has gained a major role in the therapeutic algorithm of patients with COVID-19 pneumonia requiring supplemental oxygen or on mechanical ventilation. Its wide anti-inflammatory action seems to form the basis for its beneficial action, taming the overwhelming “cytokine storm”. Amid a plethora of scientific research on the therapeutic options for COVID-19, there are still unanswered questions about the right timing, right dosing, and right duration of corticosteroids. Lastly, since medicines treat patients, we urgently need more evidence on the safety of corticosteroids on specific patient populations who may be at risk for more complications.

Author Contributions: V.R. and N.R. conceived, and designed the structure of the text and approved the final version. E.K., V.C., P.S. and A.K. (Alexandra Kote), contributed to the writing of the manuscript. I.V. and A.K. (Antonia Koutsouko) have read and approved the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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