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REVIEW

Corticosteroids in SARS-COV2 infection: certainties and uncertainties in clinical practice

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ABSTRACT

Introduction: The SARS-COV-2 pandemic is a worldwide public health problem due to the large medical burden and limited number of therapies available. Corticosteroids have a rather unclear efficacy in viral non-SARS-COV-2 pneumonias and therefore their use is not universally recommended. In SARS-COV-2 pneumonia however, it is expected that they can reduce the deleterious consequences of the virus-related systemic inflammation.

Areas covered: a MEDLINE search covering the period 1995–2020 was completed to identify relevant papers. SARS-COV-2 pathogenesis is very complex and is represented by the interplay of many cytokine-driven inflammation pathways. Its most severe form so called cytokine storm, is an exaggerate reaction of the host infected by the virus rapidly resulting in multiple organ dysfunction (MODS). Corticosteroids have the potential to blunt the inflammation response in such patients, but their efficacy is not the same for all patients. Further on the certainties and uncertainties regarding the efficacy of this therapy in SARS-COV-2 pneumonia are discussed

Expert Opinion: In patients with severe SARS-COV-2 pneumonia, corticosteroids can be efficacious, but it is still not clear if they can be safely used in patients with comorbid cardiovascular disease or how the optimal duration of therapy can be established.

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1. Introduction

SARS-COV-2 pandemics is the major public health issue of this decade. This is due to its rapid worldwide spread that was witnessed at the end of 2019 and due to the fact that the related disease (COVID-19) in its most severe form is associated with an increased risk of mortality and a huge burden on the healthcare facilities (mostly on intensive care units). One of the explanations for the lack of control of pandemics is represented by the fact that no truly effective, specific therapies against SARS-COV-2 were available at the beginning of the pandemics. Furthermore, the major pathogenic pathways leading to severe disease (respiratory failure or even acute respiratory distress syndrome, ARDS) were also rather extrapolated from similar viruses and this made for a while the identification of therapeutic targets rather difficult.

Corticosteroids have been used in viral respiratory tract infections in a rather parsimonious manner due unclear efficacy. However, in SARS-COV-2 infection they have been extensively used in an attempt to interfere with the complex inflammatory reaction triggered by the virus and to minimize the risk of cytokine storm associated with this infection. This review is based on a literature search using Medline and considering relevant papers published between 1995 and 2020. Search terms such as 'SARS-COV-2', 'viral pneumonia', 'COVID', 'corticosteroids and viral pneumonia', 'ARDS' were used. Below discussed are the certainties and the uncertainties related to the efficacy of corticosteroids in SARS-COV-2 infection in relationship with disease pathogenesis and in comparison to that reported with other, non-COVID 19 viral respiratory tract infections.

2. Pathogenesis of SARS-COV-2 infection

SARS-CoV-2 is an extremely infectious virus, with a very rapid spread worldwide, being declared a global threat by the World Health Organization (WHO) and causing the most challenging pandemics of this century. SARS-CoV-2 is a RNA virus with a genetic structure, which is similar to that of SARS-CoV-1 and of Middle East respiratory syndrome (MERS) -CoV [1].

Nasal cavity is the point of entry in the body for SARS-Cov-2 virus. After being inhaled, the virus will enter the epithelial cells of the nasal cavity and attaches to the ACE-2 receptors. Once the virus enters the cells it begins to replicate. This is the initial asymptomatic phase which lasts for about 1–2 days. Because this process takes place in the upper respiratory tract, the response of the innate immune cells will be mild. In the next 2–14 days the common symptoms of COVID-19 start to appear: fever, dry cough, pharyngitis, shortness of breath, joint pain, and tiredness. A strong innate immune response will be caused by the movement of the virus toward the lower respiratory tract. This is the stage of the disease in which patients start to present enhanced pro-inflammatory

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Article highlights

- SARS-COV-2 infection is a tremendous and ongoing public health problem.
- This infection can have a large spectrum of clinical manifestations and of severities of the disease but severe SARS-COV-2 pneumonia is the most common form of severe disease and is associated with a significant morbidity and mortality.
- In certain persons with SARS-COV-2 infection, the host inflammatory response is upregulated as a result of virus intracellular multiplication, and this can lead to severe pneumonia and MOF including ARDS.
- In other viral pneumonias, the efficacy of corticosteroids is rather unclear or sporadic.
- Corticosteroids are used in SARS-COV-2 pneumonia in an attempt to reduce the systemic inflammation and MOF
- Based on existing evidence, corticosteroids are recommended in severe SARS-COV2 pneumonia, a daily dosage of 6 mg dexamethasone up to 10 days being indicated
- Uncertainties still surround the efficacy of corticosteroids in patients with cardiovascular comorbid conditions and their optimal duration of administration in patients with clear indication.

response that leads to viral 'sepsis' accompanied by other complications, including inflammatory lung injury, Acute Respiratory Distress Syndrome (ARDS), different organ failures, and death [2].

Unlike other beta coronaviruses SARS-CoV-2 deaths are the result of multiple organ dysfunction syndrome (MODS) and not the result of the respiratory infection itself. The explanation seems to be related to the ubiquitous distribution of the angiotensin-2 conversion enzyme (ACE-2) receptors, one of the potential target receptors for SARS-CoV-2, in the human body, they being expressed on the cell surface, in the lungs, gastrointestinal tract, vessels, brain, liver, kidneys, spleen, and skin [3]. ACE-2 receptors have been shown to be predominantly expressed in alveolar type 2 cells of lung parenchyma and in ciliated and goblet cells in the respiratory tract and this explains why the respiratory system is the main entry portal of the virus. At the same time, these receptors have a high expression in the intestinal epithelium and are also expressed in cardiac cells and vascular endothelium, which may explain digestive or cardiovascular complications in some patients. These receptors have a lower expression on monocytes and on macrophages, and this may provide a mechanism of entry into immune cells for SARS-CoV-2 [4]. Because viral replication is rapidly exponential, this may cause the apoptosis of epithelial and endothelial cell at a massive scale and also vascular leakage, resulting in the release of exuberant pro-inflammatory cytokines and chemokines [5]. Macrophage and lymphocyte pyroptosis also appears to be caused by SARS-CoV-2 disease and this might explain lymphopenia detected in most of the cases with severe COVID-19 [6–8]. The nowadays proverbial 'Cytokine storm' (or Macrophage Activating Syndrome) is a form of hyperimmune host response which can be triggered in various settings ranging from cancers to monoclonal antibody therapies [9] and is associated with increased serum ferritine, coaguloation impairment, and hepatic failure [10]. In this case, this inflammatory 'storm' is the consequence of the presence of the virus' inside macrophages, and can result in MODS including ARDS [11,12]. However it should be noted that this is a rather generic description considered in the absence of an accurate definition. MODS and high viral titers in the lung and circulatory immune cells were previously reported post mortem in individuals with SARS due to other coronaviruses [13].

2.1. SARS-COV-2 infection and related inflammation 'actors': mediators and biomarkers

After attaching and infecting the host cell SARS-CoV-2 triggers the innate immune response mediated by dendritic cells and macrophages. Viral antigenic peptides are presented to CD8 + T cells causing their activation. CD8 + T cells will cause the apoptosis and the lysis of the infected cells. Concomitantly, natural killer (NK) cells become activated and produce pro-inflammatory cytokines via signaling pathways such as nuclear factor kappa B (NF-kB) and regulatory factor interferon 3 (IRF3). Thus, neutrophils, monocytes and other pro-inflammatory cytokines are recruited at the site of infection [14].

Based on the existing clinical and epidemiological data, it was demonstrated that some of the infected people are asymptomatic carriers and show no clinical signs of the infection. Usually the elderly and those with associated comorbidities develop the severe form of the disease. This category of patients present lower than average values of leukocytes, lymphocytes and platelets, prolonged activated thromboplastin time, increased C-reactive protein values. Blood lymphocytes count decreases with disease progression.

The concentration of acute phase proteins such as CRP and ferritin, are high at admission of severe COVID-19 patients. CRP is more widely available and is a sensitive biomarker of inflammation and tissue damage that is increased at admission and during hospitalization [15].

In a retrospective cohort analysis of hospitalized COVID-19 patients, it was investigated if inflammatory biomarker levels predicted respiratory progressive impairment in patients who initially present with milder disease: it demonstrated that increases in serum C-reactive protein (CRP) preceded respiratory deterioration and intubation [16].

The exaggerated release of cytokines, such as IL1B, IL1RA, IL6, IL7, IL8, IL-2 R, TNF-alpha, known as the 'cytokine storm', is associated with the severity of the disease [17]. A particularity of this immune-inflammatory state triggered by SARS-COV-2 infection at the pulmonary level is that, although the progression toward ARDS is signaled by the increasing plasma levels of pro-inflammatory cytokines such as IL-6, this response is blunted compared to that found in non-SARS-COV-2 cohorts. This might indicate that in severe SARS-COV-2 the virus-related inflammation pulmonary injury is more aggressive and develops faster, before that related to the one resulting in MODS [9]. .

Serum IL-6 levels were identified as predictor for the need for mechanical ventilation and was associated with a high risk of ICU death [18,19].

Finally, recent reports draw the attention upon immunosuppression produced by SARS-COV-2 describing it as a T cell exhaustion syndrome, which is associated with prolonged viral shedding and with increased mortality [20]. This

immunosuppression might explain the high rates of ventilator- associated pneumonias and the risk of Aspergillus subsequent infection found in COVID-19 patients [21]

The dynamic nature of the inflammation in COVID-19 is a key pathogenic feature which parallels that of clinical course of the disease. Therefore, biomarkers of inflammation can be used to assess the severity, the prognostic of the disease or the need for treatment escalation.

3. Corticosteroids in non-COVID 19 pneumonias: limited use, limited efficacy

In this section, outcomes of corticosteroid therapy in cohorts of patients with severe respiratory pneumonia caused by various non-SARS-COV-2 viruses are reviewed. Subsequently, the uncertainties related to the use of corticosteroids in SARS-COV -2 infection are summarized. Corticosteroid therapy in viral lower respiratory tract infection has always been a matter of debate due to the rather contradicting evidence related to their efficacy. This is due to the fact that in such studies populations studied were not comparable in terms of severity of the disease and the presence of comorbid conditions, duration of corticosteroid therapy or their daily dosage.

3.1. Pandemic(pH1N1) influenza A virus

Corticosteroids are used in severe forms of seasonal influenza to speed the recovery from respiratory failure and have also been used extensively in pandemics (pH1N1) influenza occurring about 10 years ago. The data coming from relevant studies is discussed below to offer SARS-COV-2 infection a comparator for both pandemics and virus-related respiratory tract infections.

In one large cohort study (n = 2141 patients, adults and adolescents, median age 34), 30, respectively 60-days mortality rates and the risk for nosocomial infection were assessed according to the daily corticosteroid dosage. This was defined as being low-to moderate if between 25 and 150 mg, respectively, high if >150 mg of methylprednisolone or equivalents. The cohort was prospectively followed up and most of it (1160, 54.2%) had paO_2/FiO_2 < 300 mm Hg on admission, this denoting that most patients were very severe and with functional signs of ARDS. Corticosteroids were given to 1055 patients within the first 48 h (median of 6 days from symptom onset) from hospital admission, the median duration of corticosteroid therapy was 7 days, and they were found to have no significant therapeutic effect on 30 days, respectively, 60-days mortality when compared to no corticosteroids administration (HR 0.64, p = 0.33). In patients with ARDS criteria, these outcome measures were analyzed according to the daily dosage of corticosteroids, which was labeled as low or high: it was demonstrated that low to moderate doses significantly reduced the mortality rates (HR 0.49 for 30 day mortality rate and 0.51 for 60-days mortality rate), whereas the high dose had no effect. In patients with $paO_2/FiO_2 \geq 300$, corticosteroid therapy was however associated with an increase in 60 day mortality irrespective of the daily dosage (HR 3.02). The rate of nosocomial infection was 21.5 in patients receiving corticosteroids and this was significantly higher when compared to no corticosteroids group. Within the group of patients receiving corticosteroids there was a correlation of the daily dosage with the rate of nosocomial infection (16.8% in low to moderate daily dosage versus 24.8% in high dose group, p = 0.002). Nosocomial infection occurred in 19.1% of patients in the corticosteroid group compared to 4.1% in patients not receiving corticosteroids (p < 0.001). Compared with the low-to-moderate-dose corticosteroid group, more patients in the high-dose corticosteroid group experienced nosocomial bacterial infection (16.8% vs 24.8%, p = .002). In the subgroup of patients with corticosteroid therapy, higher corticosteroid dose was associated with significantly higher incidences of *P. aeruginosa* and *S. aureus* nosocomial infection compared to lower to moderate doses (4.4% versus 2, p = 0.026, 3.8 versus 1,1, p = 0.033) [22].

Corticosteroid therapy did not result in a survival benefit in another cohort of patients with severe pandemic (H1N1) influenza pneumonia (n = 372, 136 receiving corticosteroids) hospitalized in ICU (HR = 1.06, p = 0.8) [23].

The analysis of the survival outcome in patients included in the French registry of ARDS due to pandemic (H1N1) influenza included 208 patients of whom 83(39.9%) received corticosteroids (a median dose of 270 mg of hydrocortisone or equivalents for a median duration of 11 days), found that this therapy was associated with a significantly crude higher mortality rate respectively risk (33.7%versus 16.8%, HR 2,4 p = 0.004). Adjusted mortality rate controlled for ARDS severity score, use of vasopressors and underlying immunosuppression was even higher 2.82, p = 0.002). Furthermore early corticosteroid therapy initiated within the first 3 days of mechanical ventilation was found to result in higher mortality risk compared to late administration. The incidence of ICU- acquired bacterial pneumonia was higher (41% versus 26,4 p = 0.01) in the group of patients receiving corticosteroids, they also exhibiting a trend toward a significantly longer intubation and mechanical ventilation duration (17 versus 13, p = 0.07). None of the patients in the corticosteroid group was off the mechanical ventilation at day 28(compared to 8 patients in the group not receiving corticosteroids (8, p = 0.01) [24].

Similar results were reported with early corticosteroid therapy on a cohort of patients with pandemic (H1N1) influenza included in the European Society of Intensive Care Medicine registry. The cohort analyzed had 220 patients admitted to the ICU and having complete sets of data. ICU-related mortality rate was 30.5% and corticosteroid therapy was given in 126 (57.3%) of the patients at the time of ICU admission, these patients being more likely to have underlying chronic respiratory diseases compared to patients not receiving such a therapy. Early corticosteroid therapy in the ICU was associated with a significantly higher risk of hospital-acquired pneumonia (odds ratio 2.2) and of ICU death (odds ratio 3.8). Comparable results were reported in the subsets of patients with ARDS [25].

3.2. Respiratory syncytial virus

Respiratory syncytial virus can cause severe lower respiratory tract infection at extremes of age, in patients with disease- or therapy-related immunosuppression in patients with advanced chronic lung diseases. In this review, discussed

data on this virus were used as a comparator of efficacy of corticosteroids in patients with various degrees of immunosuppression.

In hematopoietic cell transplantation recipients diagnosed with upper respiratory tract infection due to respiratory syncytial virus, corticosteroid therapy was not found to be a predictor of viral disease progression to lower respiratory tract disease including pneumonia [26].

3.3. MERS

Middle East Respiratory (COVID) syndrome (MERS-COV) was diagnosed for the first time in early 2010 in Saudi Arabia, the first case presenting with pneumonia, respiratory and with multiple organ failures [27]. Local outbreaks of MERS-COV with mainly human to human in health care settings and secondarily dromedary camels to human were subsequently reported [28]. Among the risk factors for severe forms of diseases manifesting with respiratory failure or with acute distress respiratory syndrome (ARDS) identified were older age, presence of comorbidities such as cardiovascular diseases, obesity, chronic respiratory diseases, kidney failures, cancer or therapeutic immunosuppression [28]. The virus isolated in these cases was represented by a betacoronavirus of C phylogeneic lineage which uses the spike glycoprotein as the main agent to infect the host cells [28].

From a clinical point of view most frequently the disease manifests as a respiratory tract infection commonly with fever at the onset. In cases with ARDS, coinfection with bacteria such as *S. aureus* or with other viruses is a common finding. Molecular diagnosis is done via PCR method using nasal or pharyngeal swabs as biological samples. Various empiric therapies including corticosteroids were used in such patients. The data on corticosteroid efficacy in MERS infection were used in this review as a comparator based on the similarities of the coronaviruses involved.

A retrospective cohort study enrolling 309 critically ill patients with severe MERS-COV (with ARDS) efficacy of corticosteroids was evaluated. Doses of corticosteroids given were quantified in hydrocortisone equivalents (1 mg of methylprednisolone to 5 mg hydrocortisone, 1 mg dexamethasone to 25 mg of hydrocortisone and 1 mg of prednisolone to 4 mg of hydrocortisone). The primary endpoint of efficacy was represented by 90-day all-cause mortality. Secondary endpoints were represented by the time to viral clearance in respiratory secretions (measured via PCR test, negative on two consecutive occasions), ICU respectively hospital mortality rates, length of ICU respectively hospital stays. Subset analyses were performed according to corticosteroid daily doses (high if >300 mg of hydrocortisone or equivalent and low if ≤300 mg) and according to the day of corticosteroid initiation after ICU admission (within the first 7 days, respectively, after 7 days), both these subsets being compared to that of patients admitted to ICU but not receiving corticosteroids. From the 309 patients found eligible for this analysis, 151 (48.9%) received corticosteroid therapy during ICU stay and did not differ in terms of age, gender, source of infection, days from symptoms onset to emergency room or ICU admission, SOFA score, other measures of ARDS severity and other baseline characteristics. However patients in the corticosteroid group were significantly more likely to have at least one comorbid disease compared to no-corticosteroid group (diabetes, chronic respiratory diseases etc). In terms of types of corticosteroids used, hydrocortisone was the most commonly given (103/151, 68.2%), followed by methylprednisolone 61/151 (40.4%). Corticosteroids were started about 3 days (median duration) from ICU admission, given at a median dose of 300 mg hydrocortisone or equivalents and for a median duration of 7 days. Corticosteroid use was associated with a higher crude 90 day mortality rate (74,2% versus 57.6%, $p = 0.002$), longer ICU respectively hospital stays (ICU 12.5 versus 7 days, $p < 0.0001$; hospital 21 versus 15 days, $p = 0.0006$). Patients treated with corticosteroids had a significantly lower chance of viral clearance (HR = 0.35, $p = 0.005$) alike patients treated with higher doses of corticosteroids versus no corticosteroid treatment (HR = 0.26, $p = 0.02$) or patients treated with lower doses versus the same control group (HR = 0.41, $p = 0.02$). Early corticosteroid initiation was associated with the same significantly delayed viral clearance when compared to no such therapy (0.23, $p = 0.004$) [29]

3.4. SARS-COV

Severe acute respiratory disease coronavirus (SARS-COV) was reported to cause an outbreak of respiratory tract infections in early 2000 initially in China which subsequently spread in other Asian countries and in the USA. There were more than 8000 cases and over 700 deaths worldwide. The virus causing this was identified as a crown-like RNA virus which was transmitted from humans or animals such as bats or civet cats [30,31].

Corticosteroids were recommended to be used in patients with SARS-COV but the evidence supporting their use is not conclusive. This is due to the fact that studies focusing on this issue evaluated various dosages of corticosteroids and in some cases the efficacy of a combined regimen represented by antivirals and corticosteroids.

It is the case of a study enrolling 138 SARS-COV patients which demonstrated that ribavirin+corticosteroids (low initial dose) produce a therapeutic response in 18.1% of them. Corticosteroids (methylprednisolone) was used by 107 patients. Therapeutic response was defined as defervescence for at least 4 consecutive days and regression of lung infiltrate by more than 25% and absence of fever and presence of oxygen independence by day four. The increased serum C reactive protein at admission independently predicted the use of corticosteroids (odds ratio 2.18 per each 10 mg/dl increase). Mortality rate was 10.9% [32].

Similarly when viral clearance was evaluated in 16 non-ICU patients of whom 9 received early (about 4.8 days from fever onset) corticosteroid therapy (hydrocortisone). This therapy was found to be associated with delayed viral clearance (12 days versus 8 days in non-corticosteroid users) and with higher viral load at the second respectively third week of disease [33].

In the cohort of SARS patients admitted in Hong Kong (1287 patients, 1188 of them receiving corticosteroids. It was demonstrated that mortality rate varied according to

corticosteroid regimen, being the lowest in patients receiving low dose prednisone or high doses of methylprednisolone. Analysis of the relationship between the severity of the disease and the type of corticosteroid regimen demonstrated that high-dose methylprednisolone group was more severe with the highest percentage of cases of ARDS, and the mildest disease was found in the group receiving pulsed corticosteroids. Corticosteroid regimens were also found to be associated with different mortality risks, for example intravenous hydrocortisone or pulsed corticosteroid therapy, that were associated with higher mortality risk compared to methylprednisolone (odds ratio 3.77, p = 0.0009 respectively 2.76, p = 0.01) [34].

4. Corticosteroids in SARS-COV 2 infection: certainties

The use of corticosteroids in more severe forms of lung inflammation injury such as ARDS is supported by the data coming from studies done in this latter setting and demonstrating that even a prolonged course of corticosteroids was associated with a favorable outcome. For example, a study evaluated the effects of longer courses of corticosteroid therapy in patients with ARDS due to SARS-COV. This was a placebo-controlled study which enrolled 24 patients with severe ARDS who did not improve by the day 7 of respiratory failure. Corticosteroids were given in 16 patients (methylprednisolone 2 mg/kg daily) and the mean duration of therapy was 32 days. The primary endpoints of efficacy were the improvement in lung function and mortality, whereas the secondary endpoints were represented by the improvement in multiple organ dysfunction syndrome (MODS) and the incidence of nosocomial infection. Compared to placebo corticosteroids reduced the severity of the ARDS, improved gas exchange and decreased the MODS score (corticosteroids: lung injury severity score 1.7 versus 3, p < 0.001; paO2/FIO2 ratio 262 versus 148, p < 0.001, MODS score decrease 0.7 versus 1.8, p < 0.001) and these effects were evident by study day 10 when the number of successfully extubated patients was also found to be significantly increased compared to placebo (7 versus 0, p = 0.05). Corticosteroid therapy was also associated with significantly lower intensive care unit, respectively, in hospital mortality rates (0 versus 62%, p = 0.002, respectively, 12 versus 62% p = 0.03). Incidence of nosocomial infections was comparable in both groups [35]. However, the study included various etiologies of ARDS and a full extrapolation of its efficacy results to SARS-COV-2 setting would be inappropriate.

A meta-analysis of randomized controlled studies performed in ARDS and including a total of 1505 patients (780 receiving corticosteroids and 725 not receiving them) evaluated their effects on mortality rate according to the moment of initiation (early versus late) and according to the daily dosage (low if ≤ 2 mg/kg daily versus high >2 mg/kg daily). Irrespective of the dose and of the moment of their initiation, corticosteroid therapy was associated with shorter duration of mechanical ventilation and with a significant improvement in gas exchanges. Low dose corticosteroids was associated with a lower mortality risk (odds ratio 0.43, p = 0.006) whereas the higher dose was associated with a higher (non-significant risk) (odds ratio 1.33, p = 0.2). Early corticosteroid initiation resulted in a significant survival benefit (odds ratio for mortality 0.61, p = 0.005) [36].

Since the ARDS can be the expression of the most severe lung inflammation encountered in SARS-COV-2 infection, the therapeutic benefits overall demonstrated in ARDS irrespective of the underlying cause can be supportive in the narrower SARS-COV-2 setting.

The rather unconvincing efficacy demonstrated in other viral respiratory tract infections, corticosteroids use SARS-CoV -2 infection made the consideration of this therapy debatable from the start of COVID-19 pandemic.

The use of corticosteroids brings many benefits such as inhibiting inflammation, but their administration affects the body's immune response thus increasing the risk of infection. The occurrence of side effects such as hyperglycemia, abdominal obesity, infection, mood disorders, osteoporosis, hypertension, and glaucoma, depends on the dose administered and the duration of therapy [37].

Based on extrapolation of the therapeutic indication of corticosteroids from non-COVID respiratory tract infection, earlier reports suggested that these should be given in the more severe forms of disease. Due to their anti-inflammatory and immunomodulatory properties, corticosteroids appear to be an obvious potential therapy for severe forms of COVID-19, because of their ability to suppress the upregulated inflammation [38]. Table 1 summarizes the existing evidence on clinical efficacy of corticosteroids in SARS-COV-2 pneumonia.

In one of the first reports on SARS-COV-2 infection, the proportion of patients receiving corticosteroids was significantly higher in patients admitted to the ICU compared to those who were hospitalized in non-ICU wards, and the presence of this therapy can be interpreted as an indirect 'marker' of disease severity [39].

In fact, an initial report on intravenous methylprednisolone given as 40 mg twice daily for 3 days followed by 20 mg twice daily for 3 days given in patients (n = 85) with severe COVID-19 pneumonia (i.e., associated with gas exchange impairments and with severe systemic inflammation) showed that compared to standard of care corticosteroids could significantly reduce the risk of mortality, of admission to intensive care unit and of noninvasive ventilation need (combined risk ratio in intention to treat analysis 0.55, p = 0.024), in those patients aged more than 72 year the therapeutic effect being also statistically significant (per protocol analysis risk ratio 0.61, p = 0.0037). Corticosteroids were also associated with a significant reduction in systemic inflammation (serum C reactive protein) [40].

In a study evaluating the effects of short courses of low-to moderate doses of corticosteroids (methylprednisolone 0.5–1 mg/kg/daily for 3 days), it was found that in non-critically ill patients with severe pneumonia (n = 213), this regimen was associated with less likelihood of care escalation (need for mechanical ventilation, disease progression to critically ill state, 34.9 versus 54.3% p = 0.005), significant shorter duration hospitalizations (5 versus 8 days, p < 0.001). Corticosteroid therapy was also associated with a significant reduction in mortality rates which were 26.3% for standard of

Table 1. Overview of the main clinical studies considering the corticosteroid therapy in patients with SARS-COV-2 infection.

Study		Saple size and COVID-19 severity	Corticosteroid regimen	Primary endpoint of efficacy/effect	Effect on viral clearance	Effect on mortality
Coral et al	[40]	85, severe COVID pneumonia	Methylprednisolone 40 mg twice daily for 3 days followed by 20 mg twice daily for 3 days	The need for ICU, noninvasive ventilation-reduced	Not considered	risk ratio in intention to treat analysis 0.55 and 0.61 in those patients over 75 years of age
Fadel et al	[41]	213 severe non critically ill COVID-19 pneumonia	Methylprednisolone 0.5–1 mg/kg/ daily for 3 days	Care escalation (progression to critically ill, need for mechanical ventilation, mortality)-reduced	Not considered	Reduced mortality rates 26.3% with standard of care versus 13.6% in corticosteroid group
The Writing Committee for the REMAP-CAP Investigators	[42]	137,146,101	Hydrocortisone 50 or 100 mg every 6 day for 7 days, hydrocortisone 50 mg every 6 hours (for confirmed shock), no corticosteroid	Number of organ support free days in the ICU over the first 21 days	In favor of corticosteroids, trial early terminated	Mortality rates respectively 30%, 26%, and 33% for each of the three regimens
Recovery Collaborative Group	[45]	6452(2104 in dexamethasone group) various severities (COVID-19 requiring hospitalization	Dexamethasone 6 mg/daily up to 10 days	Mortality rate within the first 28 days from randomization-reduced	Not considered	Mortality rate 25.7% in control group and 22.9 with dexamethasone $P < 0.001$
Li Q et al	[50]	475 non-severe COVID 19	Methylprednisolone 20–40 mg/ daily for a maximum of 5 days	Progression to severe disease or death – more likely if corticosteroids were used	Significantly prolonged (18 versus 11 days)	1.8% in corticosteroid group, 0% in no corticosteroid group, $p = 0.3$
Xu et al	[51]	113 non-severe COVID 19	Corticosteroids, various regimens	Not designed to measure efficacy	Significantly prolonged in patients under corticosteroids	
Li TZ et al	[52]	101 various severitied hospitalized COVID-19	Corticosteroids, various regimens	Not designed to measure efficacy	Significantly prolonged in patients under corticosteroids (OR = 6.3)	Overall 3,3 (0 for those with viral shedding lasting less than 11 days, respectively 6.5% for those with a viral shedding lasting more than 11 days
Tomazzini et al	[46]	299 moderate to severe SARS-COV2(151 in dexamethasone arm, 148 in control arm	Dexametasone intravenous 20 mg/ daily for 5 days followed by 10 mg the following 5 days or up to ICU discharge	Number of ventilator free days at 28 day from admission-increased	Not considered	All cause mortality rate at 8 days was 56.3% in the dexamethasone group and 61.5% in the control group ($p = 0.8$)
Salton et al	[53]	173 severe COVID-19 pneumonia	Methylprednisolone- loading dose of 80 mg intravenous bolus, followed by daily infused identical doses at least 8 days, could be further prolonged based on severity	Care escalation due to disease progression (ICU, mechanical ventilation) or death-significantly reduced	Not considered	Mortality rates 7.2% in corticosteroid group compared to 23.3% in the standard of care group, ($p = 0.005$)

care group versus 13.6% in corticosteroids group ($p = 0.024$) [41].

Hydrocortisone was also evaluated in another randomized study in severe SARS-COV-2 patients. The regimens compared were a fixed 7 day course of intravenous hydrocortisone (50 mg or 100 mg every 6 hours, 137 patients) a shock-dependent course (50 mg every 6 hours, 146 patients) or no hydrocortisone(101 patients). The primary endpoint was represented by the number of organ support free days over the first 21 days, which had higher chances to be larger with each of the corticosteroid regimens. The trial was stopped early however, for unclear reasons [42]

More recently, dexamethasone was evaluated for its efficacy in severe SARS-COV-2 infection. Before it supportive evidence can be considered the findings of a recent study evaluating the efficacy of dexamethasone in patients with ARDS of various etiologies: the regimen was 20 mg/day for the first 5 days followed by 10 mg/daily for the next 5 days and the primary endpoint was represented by the number of ventilator-free days at 28 days and the secondary endpoint was all cause mortality 60 days after randomization. From the 277 patients enrolled dexamethasone was received by 139 patients. Dexamethasone therapy significantly increased the number of ventilator free days (difference of 4.8 days, $p < 0.0001$ in favor of dexamethasone). Mortality rate was significantly lower in the corticosteroid group (21% versus 36% in control group, $p = 0.0047$ for the treatment difference. The incidences of adverse events were comparable in both

groups with hyperglycemia (76% versus 70%), secondary infections in the ICU (24% versus 25%) being the most commonly reported. The safety monitoring board decided premature termination of the trial due to low enrollment rate [43].

Dexamethasone is recommended by the existing guidelines as the first line corticosteroid in the treatment of moderate or severe SARS-COV-2 pneumonia according to the existing guidelines [44]. The available clinical efficacy data support its use for this condition. The RECOVERY study is an open label study on the efficacy of dexamethasone (6 mg/daily up to 10 days) in hospitalized COVID-19 with the largest cohort (2104 patients in the dexamethasone group and 4321 in the control group) [45]. The primary endpoint was represented by mortality rate within the first 28 days after randomization. The secondary endpoints included time to hospital discharge, time to mechanical ventilation, duration of ventilation, the need for hemodialysis or hemofiltration and the occurrence of major cardiac arrhythmia.

Dexamethasone was associated with a significantly lower mortality rate (22.9% versus 25.7%, $p < 0.001$) and the survival benefit was found to be the highest in patients receiving at baseline ventilator support (who were younger than those not requiring it and who had a longer duration of respiratory symptoms) (29.3% versus 41.4%) and in those on supplemental oxygen therapy (23.2% versus 26.2%). Similar findings were reported in a post-hoc analysis performed in a subset of 5698 patients with SARS-COV-2 positive test at baseline. Hospitalization duration was shorter in patients on dexamethasone (12 versus 13 days) who were also more likely to be discharged before 28 days from referral (rate ratio 1.1). Dexamethasone therapy was associated with a lower likelihood of the mechanical ventilation or death in patients not being on ventilator support at baseline (risk ratio 0.92) this effect being larger in those who at randomization were receiving supplemental oxygen therapy.

In a randomized study performed in 299 patients with moderate to severe SARS-COV-2 referred to ICU compared a regimen consisting of 20 mg intravenous dexamethasone daily for 5 days followed by 10 mg daily for 5 days or until ICU discharge added to standard of care to this latter alone. Primary endpoint was represented by ventilator free days during the first 28 days of ICU. Dexamethasone was associated with more days off the ventilator (6.6 compared to 4 in the control group, $p = 0.04$) but had no significant effect on all cause mortality at 28 days (included as a secondary endpoint). In fact all cause mortality rate at 28 days was 56.3% in dexamethasone group and 61.5% in the standard of care group ($p = 0.8$) [46].

These findings were preliminarily reported and further results are expected in the future for mortality rate at 6 months from randomization and for the other secondary endpoints [45].

All these data suggest that corticosteroids are effective in patients with more severe SARS-COV-2 pneumonia and that they shouldn't be discretionarily used in all patients with this infection. This is in line with the recommendations of various expert panels and which are summarized in Table 2[44,47,48].

Table 2. Recommendations of expert panels for the use of corticosteroids in patients with SARS-COV2 pneumonia[44.47].

- Indication for using corticosteroids should be based on an a priori risk-benefit analysis.
- Dexamethasone 6 mg once daily or equivalents (prednisone 40 mg, methylprednisolone 32 mg, hydrocortisone 160 mg) is the daily dosage recommended.
- Hydrcortisone having the shorter half-life should be used in patients with SARS-COV2 and sepsis.
- Corticosteroids are recommended in patients with severe SARS-COV2 infection requiring high-flow oxygen and/or mechanical ventilation and as an alternative to remdesivir in patients with hypoxemia not requiring high oxygen flows.
- In patients with non-severe SARS-COV 2 infection corticosteroids use should rather be restrictive, and not recommended in patients without hypoxemia or with no need for hospitalization
- A short course ≤ 7 days being indicated.

5. Corticosteroids in SARS-COV 2 infection: uncertainties

The use of corticosteroids in SARS-COV-2 infection is still associated with various uncertainties most of them related to their efficacy in patients with non-severe SARS-COV-2 infections and in patients with comorbid advanced cardiovascular disease and to the optimal duration of corticosteroid therapy.

'The sooner, the better' paradigm seems to be effective regarding the decision for corticosteroids treatment as early low-dose treatment is associated with reduced mortality in severe COVID-19 patients in contrast with high-doses administered later that seem to have no beneficial effect either on treating ARDS consequences or improving patient's outcome whatsoever [49].

In a recent retrospective analysis performed on a cohort of patients with SARS-COV-2 with less severe forms of the disease, there were 55 patients receiving corticosteroids and 420 not receiving them considered as a primary outcome the rate of patients progressing to severe disease or death and as secondary outcomes presence and persistence of fever duration of viral clearance, duration of hospitalization and the use of antibiotics. Corticosteroids were given at low dose (methylprednisolone dose 20–40 mg/daily for a maximum of 5 days) and were initiated at a median lag time of 2 days from hospital admission. Progression to severe disease was more common in patients receiving corticosteroids (12.7% versus 1.8%, $p = 0.028$). Patients receiving corticosteroids had a longer-lasting fever (5 versus 3 days, $p < 0.001$), a slower viral clearance (18 versus 11 days, $p < 0.001$), longer hospitalizations (23 versus 15 days, $p < 0.001$), more frequent need for at least two antibiotics respectively for antifungal therapy (38.2% versus 12.7%, $p = 0.002$; 7.3versus 0, $p = 0.042$). Mortality rates were comparable, ie 1.8% in the corticosteroid group and 0% in the standard of care group, ($p = 0.3$) [50]. In the same cohort, corticosteroid therapy was also associated with a prolonged viral shedding (>15 days) inpatients with SARS-COV-2 infection [51]. Similar results were reported in 66 patients in whom corticosteroid therapy was the most significant risk factor for prolonged viral clearance (OR 6.3). In the same study mortality rate was higher in patients with prolonged viral shedding

compared to those who were cleared off the virus earlier (0% versus 6.5% in those with viral shedding lasting more than 11 days) [52].

As far as the optimal duration of corticosteroid therapy is concerned, the shorter durations were supported by some of the studies but a more recent one advocates the early use of longer low dose corticosteroid courses in patients with severe SARS-COV-2 pneumonia: in fact in a cohort of 173 patients a methylprednisolone-based regimen with a loading dose of 80 mg intravenous bolus, followed by daily infused identical doses at least 8 days and continued at a quarter of the dose until correction of inflammation and of gas exchange, was studied. This regimen was found to result in less need for ICU referral, lower mortality rates (7.2% in corticosteroids arm versus 23.3% in the standard of care, $p = 0.005$), less frequent use of mechanical ventilation and in more rapid weaning from it at the end of the 28 day study period [53]. There for it is still uncertain what optimal duration should be for a corticosteroid course and probably the severity of gas exchange impairment, the extension of pulmonary lesions on CT scan and the severity of the systemic inflammation should be the best criteria to decide on this issue.

For the efficacy and safety of corticosteroids in patients with advanced cardiovascular condition further research is needed to document the optimal dose and duration. For such patients considering the use of corticosteroids via inhalation route would be a relevant issue to clarify.

It is hoped that the upcoming studies are going to yield less heterogeneous findings, which should allow a more accurate conclusion on the efficacy and safety of corticosteroids and on the characteristics of the disease associated with maximal therapeutic benefit. Many of the existing uncertainties might be also due to this data behavior and therefore the pooled interpretation should be rather prudent [54]

6. Conclusions

The data presented in this review suggests that the role of corticosteroid treatment in SARS-CoV-2 virus infection should be reconsidered as a valuable option. Given the pathophysiology of the disease, corticosteroids could have beneficial effects on both hyperinflammation and ARDS as COVID19 seems to be a steroid responsive disease. In the same time, this anti-inflammatory and immunomodulatory treatment is easily accessible, has proven benefits, and the associated costs are quite low. Of course, when administering corticosteroid therapy, the risk-benefit ratio of this type of treatment must be considered, depending on each patient.

7. Expert opinion

The evidence above discussed favors the use of corticosteroids in patients with severe forms of SARS-COV-2 pneumonia. They are able to reduce the deleterious effects of the inflammation which virus triggers in the host at various levels including pulmonary or nervous systems.

Still, the use of corticosteroids in this infection is associated with some important uncertainties: these are related to the severity of the disease, to the timing of corticosteroids initiation, to the daily dose, to the duration of the course and to the appropriateness of use in comorbid conditions such as advanced cardiovascular diseases or diabetes .

In terms of severity stage of SARS-COV-2 infection in which systemic corticosteroids are the most appropriate to be used, what is certain that they are useful in reducing mortality and the burden of disease in patients with severe SARS-COV-2 pneumonia, respiratory failure and ARDS.

Currently, there is no criteria to establish which is the best period in the disease course to initiate corticosteroid therapy, and which are the biomarkers of inflammation, which can show us that the systemic inflammation is at a level worth being subsequently severed as a result of corticosteroid administration. Among the studies considered in this review, some of them performed in different viral settings examine the so called early (at the time of admission) versus late initiations of corticosteroid therapy without however being very conclusive. Furthermore, in SARS-COV-2 infection robust data (best if coming from randomized controlled trials or comparisons in similar cohorts) on this approach are not available yet.

In terms of daily dosage, i.e., if a low dose is to be used or a high dose is better, or when each of them is the most appropriate, again it is uncertain. First of all, there is no unanimous definition of what a low dose versus high dose should mean, the studies discussed in this draft having each its specified threshold values to differentiate these two types of dosages.

Duration of the corticosteroid course is another uncertainty which is important to be clarified. It is known that even 'shorter' exposure to corticosteroids is associated with an increased risk of developing related side effects. This was demonstrated in a retrospective 3 year cohort analysis performed in the USA in more than 300,000 patients whom were prescribed corticosteroids for a median period of 6 days (46.9% of the prescriptions) and which identified high risks of sepsis, venous thromboembolism and fracture (rate ratio 5.3 respectively 3.33 and 1.87) within the first 30 days of corticosteroid initiation, diminishing over the next 60 days but still remaining significantly high afterward for a daily dose of less than 20 mg prednisone or equivalents [55].

In patients with comorbid conditions which are in themselves risk factors for increased systemic inflammation, corticosteroids use should be decided and implemented with caution. It is the case of diabetes, a major risk factor for severe SARS-COV-2 infection and a chronic disease in which corticosteroid use for associated conditions is usually very restricted in terms of duration and daily dosages. This is due to the fact that in this setting corticosteroids can actually as pro-inflammatory agents in an indirect manner, based on the loss of appropriate glycemic control.

It is very well known that corticosteroids use is associated with side effects such as delirium, hospital acquired infections (bacterial, fungal and viral), myopathy and they are documented in other settings of long-term therapy. It is necessary

however to monitor the safety of this therapy in SARS-COV-2 patients this not being considered in the existing trials.

Optionally, it might be possible that in patients with milder forms of SARS-COV-2 in whom systemic administration of corticosteroids is contraindicated nebulized (inhaled) corticosteroids might be an option. This might be the case for example of asthma/chronic obstructive pulmonary disease patients having comorbid diabetes and in whom in this way the risk of loss of control of the metabolic disease can be mitigated [56].

Also it would be interesting to evaluate the combined efficacy antivirals+ corticosteroids. In fact an adaptive trial comparing the efficacy of an anti Janus kinase baricitinib added to remdesivir with remdesivir+dexamethasone is currently underway [57].

Given the efficacy of shorter courses of corticosteroids in patients with SARS-COV-2 infection supported by both 'pathogenic' rationale of use and by the demonstrated improvement of the relevant outcome measures, they can be used in an attempt to reduce the mortality risks and the inflammation load but a better characterization of the population subset which would most benefit from such a therapy is still necessary.

Declaration of interest

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