INTRODUCTION

The knowledge about SARS-Cov-2 infection emphasises the correlation between severe complications (acute respiratory distress syndrome, acute heart injuries, acute kidney complication) and cytokine storm (CS) (Chan, Wong et al. 2020, Huang, Wang et al. 2020, Sun, Lu et al. 2020). CS refers to the excessive and uncontrolled release of pro-inflammatory cytokines caused by a variety of diseases, including infectious diseases, rheumatic diseases and tumour immunotherapy. Clinically, it commonly presents as systemic inflammation, multiple organ failure, and high inflammatory parameters.

GCs have an overall immunosuppressive effect, and these are often used in patients with inflammatory and autoimmune diseases. GCs are nowadays preferred to treat and relief COVID-19 symptoms for their ability to stop the cytokine storm and to prevent lung fibrosis (Yuen, Ye et al. 2020).

The clinical use of drugs could be evidence-based provided by good-quality randomised controlled trial (RCT). Anecdotal experiences or physiopathological findings have limited scientific validity. With this narrative review, we want to resemble the clinical evidence about the efficacy of GCs for patients with COVID-19.

Glucocorticoids For The Treatment Of Sars-Cov-2

Cao et al. (Cao, Tu et al. 2020), in their cohort of patients with COVID-19, reported a rate of acute respiratory distress...
syndrome (ARDS), acute infection, and acute cardiac injury, respectively of 19.6%, 16.7% and 14.7%. The rate of ICU admission was 17.6%, and the overall mortality rate was 16.7%. The most common cause of death was multiple organ dysfunction syndrome (MODS), with a rate of 58.8%. MODS could be due to the CS, triggered by excessive T cell activation, as suggested by pathologic examinations of COVID-19 with multiple organ failure (Wang, Hu et al. 2020, Xu, Shi et al. 2020). These pathophysiological findings seem to justify the clinical use of GCs as drugs that can “turn off” the systemic inflammatory response.

However, no RCT was published on this issue. Russell et al. (Russell, Millar et al. 2020) stated that GCs treatment should not be used for the treatment of lung injury induced by SARS-CoV-2 infection or shock outside of a clinical trial.

Despite the lack of clear evidence, the Surviving Sepsis Campaign guideline on the management of critically ill patients with COVID-19 (Alhazzani, Moller et al. 2020) suggests the use of low-dose GCs in two clinical settings.

The first one includes “shock-reversal” in patients with septic shock (weak recommendation, very low-quality evidence). The second setting is characterised by patients with respiratory failure and ARDS (weak recommendation, low-quality evidence). In mechanically ventilated critical patients with COVID-19 and respiratory failure (without ARDS), the guideline does not recommend the routine use of systemic GCs (weak recommendation, low-quality evidence).

To date, three RCTs (registration number ChiCTR2000029386, ChiCTR2000029656, and NCT0424459) on the role of GCs in the COVID-19 patients setting are ongoing (Zhang, Wang et al. 2020). However, it is essential to underline that there were significant differences in the primary endpoints of these trials. Only one RCT (ChiCTR2000029386) analyses mortality rate and clinical improvement in a population of 48 patients with the severe form of SARS-CoV-2 infection (Zhou, Qin et al. 2020). In contrast, the other two are RCTs with clinical endpoints like ECG and chest imaging modifications, development of complications, lung injury score.

Despite these aspects, we hope that the results could be to help the clinicians to support the clinical choice of GCs administration in patients with COVID-19.

**Glucocorticoids for the Treatment of Sars and Mers**

SARS-CoV-2 is a beta coronavirus, belonging to the same family of the middle east respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV)(Rabaan, Al-Ahmed et al. 2020). When compared with SARS-CoV and MERS-CoV, the SARS-CoV-2 showed a genetic similarity of 79% with SARS-CoV and 50% with MERS-CoV. Furthermore, the receptor-binding domain (S1) of SARS-CoV-2 was closely similar to the S1 domain of SARS. Protein modelling studies showed that the outer subdomain of the SARS-CoV-2 receptor-binding domain closely related to the SARS. This observation also indicates that similar to the SARS-CoV, the SARS-CoV-2 may also utilise ACE2 as receptor(Lu, Zhao et al. 2020).

These analogies among different viral agents could be useful to recover evidence on the clinical efficacy of GCs used in the previous RCT during SARS and MERS epidemic.

In the SARS epidemic in 2003, GCs were the basic medication of the immunomodulatory therapy and improved the early fever, promoted the absorption of pneumonia, reaching better oxygenation. However, some studies did not show beneficial effects with GCs, or even adverse reactions or delayed virus clearance, leading to the deterioration of the disease (Ho, Ooi et al. 2003, Auyeung, Lee et al. 2005, Chen, Tang et al. 2006, Yam, Lau et al. 2007). One systematic review of studies on patients with SARS-CoV, including 29 studies documenting GCs use, found 25 studies that were inconclusive regarding the role of the adjunctive use of GCs, and four studies demonstrated that the use of systemic GCs in SARS patients could cause possible harm (Stockman, Bellamy et al. 2006).

Many possible complications of GCs use, such as profound immunosuppression, with the potential emergence of severe commensal and other viral and bacterial infections, invasive fungal infections, osteonecrosis and psychosis may occur with prolonged and high-dose glucocorticoid therapy (Wang, Ding et al. 2003, Hong and Du 2004, Lee, Wing et al. 2004, Griffith, Antonio et al. 2005, Tai 2007).

GCs therapy was also commonly used for critically ill patients with MERS. Many patients with severe MERS were treated with systemic high-dose GCs intending to reverse the progression of respiratory distress and to prevent lung fibrosis. However, this approach has not been proven to be successful (Who Mers-Cov Research 2013). One study of 314 symptomatic MERS patients, found that GCs use was associated with increased mortality in these patients (Alfaraj, Al-Tawfiq et al. 2019). A retrospective cohort study compared 151 patients receiving GCs with 158 patients in the control group, found no difference in mortality between the two groups. However, GCs therapy group presented a delayed MERS-CoV RNA clearance, after adjustment for baseline and time-varying confounding factors (Arabi, Mandourah et al. 2018).

However, there are doubts about the clinical efficacy of GCs therapy in these syndromes (Booth, Matukas et al. 2003, Yam, Lau et al. 2007, Arabi, Mandourah et al. 2018).

**CONCLUSION**

Although the administration of GCs could be justified by physiopathological findings of cytokine storm and previous clinical study on SARS and MERS, in the literature, there is no evidence on the clinical role of GCs and data by the previous RCT were inconclusive. Three Chinese RCTs on the role of GCs for the treatment of SARS-CoV-2 infection are ongoing.

Despite the different endpoints selected, we hope that these RCTs could provide better clinical information on the therapeutical role of GCs in patients with SARS-CoV-2 infection.

**Authors Contributions**

All the authors wrote the article.

**Conflict of Interest**

The authors declare no conflict of interest.
References


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