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

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Review

Glucocorticoids and COVID-19

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ABSTRACT

Coronavirus Disease 19 (COVID-19) is associated with high morbidity and mortality rates globally, representing the greatest health and economic challenge today. Several drugs are currently approved for the treatment of COVID-19. Among these, glucocorticoids (GCs) have received particular attention due to their anti-inflammatory and immunosuppressive effects. In fact, GC are widely used in current clinical practice to treat inflammatory, allergic and autoimmune diseases. Major mechanisms of GC action include inhibition of innate and adaptive immune activity. In particular, an important role is played by the inhibition of pro-inflammatory cytokines and chemokines, and the induction of proteins with anti-inflammatory activity. Overall, as indicated by various national and international regulatory agencies, GCs are recommended for the treatment of COVID-19 in patients requiring oxygen therapy, with or without mechanical ventilation. Regarding the use of GCs for the COVID-19 treatment of non-hospitalized patients at an early stage of the disease, many controversial studies have been reported and regulatory agencies have not recommended their use. The decision to start GC therapy should be based not only on the severity of COVID-19 disease, but also on careful considerations of the benefit/risk profile in individual patients, including monitoring of adverse events. In this review we summarize the effects of GCs on the major cellular and molecular components of the inflammatory/immune system, the benefits and the adverse common reactions in the treatment of inflammatory/autoimmune diseases, as well as in the management of COVID-19.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) virus and its variants are the cause of coronavirus disease 2019 (COVID-19). This infectious disease is responsible for millions of deaths and has stimulated great efforts to identify therapeutic strategies in many laboratories and clinical centers around the world. The effects of the disease range from non-symptomatic infection and mild symptoms to severe pneumonia, acute respiratory distress syndrome (ARDS) and fatal multi-organ failure [1,2]. After the interaction of the viral spike protein (S) with angiotensin-converting enzyme 2 (ACE2) receptors, an inflammatory response is activated in many tissues and organs including, among others, blood vessels in the lungs. The activation of numerous components comprising cells and soluble factors of the innate and adaptive responses leads to systemic inflammation. Interleukins (ILs) and other cytokines and chemokines are released and, depending on the levels produced, they may cause a dysregulated inflammatory response and a cytokine storm inducing multiple organ failure, ARDS and worse prognosis [3,4].

Vaccinating the global population against COVID-19 has been the main strategy to contain the pandemic (WHO (2021), Coronavirus disease (COVID-19): Herd immunity, lockdowns and COVID-19, https://www.who.int/news-room/q-a-detail/herd-immunity-lockdowns-and-covid-19). Beyond the use of vaccines, novel therapeutic options, such as convalescent plasma and potentially efficacious anti-SARS-Cov-2 monoclonal antibodies and antiviral drugs are under investigation and have already been used to directly control SARS-Cov-2 and the resulting disease (https://www.covid19treatmentguidelines.nih.gov/ assessed 19/3/2022).

Drugs that have been firstly used in the management of COVID-19 include, among many others [5], antibiotics such as antimalarials, heparin to manage thromboembolic events, antiviral agents formerly

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employed for other infectious disease as well as new ones, such as remdesivir, molnupiravir, and the combination of nirmatrelvir and ritonavir (Paxlovid™), non-steroidal anti-inflammatory drugs (NSAIDs), interferon (IFN)-α, -β and -λ, inhibitors of cytokines or of their receptors, such as IL-6, IL-1 and granulocyte macrophage-colony stimulating factor (GM-CSF), Janus kinase (JAK) inhibitors and glucocorticoids (GCs) [6–12]. Moreover, the relevance of agents exerting both anti-viral and anti-inflammatory activities has been described since the beginning of the pandemic in China. Clearly, the use of so many drugs, even in combination therapies, has to be appropriate and recently important

Table 1
Summary of glucocorticoid studies in patients with COVID-19.

Study reference and country	Design	Population	Interventions	Outcomes
[4], China	Retrospective observational study, single-center	201 patients, the median age was 51 years, 64 % men, 36 % women	Methylprednisolone	The GC administration appears to have reduced the risk of death in patients with ARDS 21/50 (46 %) vs. 21/34 (61,8 %)
[173], Netherlands	Prospective observational study, single-center	172 patients, the median age was 67 years, 79 % men, 21 % women	Methylprednisolone 250 mg IV (day1), 80 mg. (days 2–5)	High- dose GC decreased hospital mortality: GC group 10/86 (11,6 %) vs. control group 1/9 (38,4 %)
[174], Iran	Randomized clinical trial, multicenter	62 adult patients hospitalized with severe COVID-19, the median age was 58,5 years, 62,9 % men, 37,1 % women	Methylprednisolone 250 mg IV daily for 3 days prior to intubation	Mortality rate was significantly lower in the methylprednisolone group Compared with controls (5,9 % GC vs. 42,9 % usual care); Improved clinical recovery (94.1 % GC vs. 57.1 % usual care)
[175], France	Retrospective observational study, single-center	62 adult patients with COVID-19 severe pneumonia, the median age was 61 years, 75,7 % men, 24,3 % women	No indications for GC therapy	GC therapy lowered the risk of intubation (22.5 % GC vs. 71.8 % controls)
[19], United Kingdom	Randomized controlled trial, multicenter	4321 hospitalized patients, the median age was 66 years, 64 % men, 36 % women	Dexamethasone 6 mg/day IV or oral up to 10 days	Reduced mortality at day 28 was significant (29.3 % GC vs. 41.4 % usual care) in severe COVID-19 patients receiving invasive MV
[167], Spain	Retrospective observational study, single-center	463 COVID-19 patients with severe ARDS, the median age was 58 years, men 68,4 % women 31,6 %	Methylprednisolone 1 mg/kg/day (no different outcome w or w/o initial GC pulse therapy)	Survival of COVID-19 with ARDS is higher in patients treated with GC compared with controls (86,1 % GC vs. 76,1 % usual care)
[147] CoDEX, Brazil	Randomized controlled trial, multicenter	299 hospitalized COVID-19 patients with moderate to severe ARDS, receiving invasive MV, the median age was 61 years, men 59,6 % women 40,4 %	Dexamethasone 20 mg/day IV for 5 days, then 10 mg/day IV for other 5 days	GC treatment reduced mortality (85/151 (56,35 %) GC vs. 91/148 (61,55 %) usual care) and increased the number of days alive and free of MV. Trial stopped prematurely following information from RECOVERY study.
[145] GLUCOCOVID, Spain	Randomized controlled trial, multicenter	64 adult patients hospitalized with COVID-19 for at least 7 days of symptoms and requiring oxygen without IC or MV, men 61 % women 39 %	Methylprednisolone 40 mg IV every 12 h for 3 days, then 20 mg IV every 12 h for other 3 days	Methylprednisolone did not reduced mortality significantly compared with controls. Trial stopped prematurely following information from RECOVERY study.
[149] MetCOVID, Brazil	Randomized controlled trial, single center	393 adult patients hospitalized with COVID-19 requiring supplemental oxygen or invasive MV, men 64,6 %, women 35,4 %	Methylprednisolone 0.5 mg/kg IV every 12 h for 5 days	Methylprednisolone did not reduced mortality significantly compared with controls at day 28 (72/194 (37,1 %) GC vs. 76/199 (38,2 %) control). Survival benefit observed with methylprednisolone treatment in patients over 60 years. Trial stopped prematurely following information from RECOVERY study.
[144] REMAP-CAP (2020), Europe, Usa, Canada, Australia, New Zealand, Saudi Arabia	Randomized controlled trial, multicenter	384 hospitalized patients with severe COVID-19, 50–64 % required MV, the median age was 60 years, 71 % men, 29 % women	Hydrocortisone 50 mg or100mg IV every 6 h for 7 days, or a shock-dependent course of 50 mg every 6 h for duration of shock	Hydrocortisone treatment did not reduced mortality significantly compared with controls (78/278 (28 %) GC vs. 33/99 (33,3 %) usual care). Trial stopped prematurely following information from RECOVERY study.
[146] CAPE COD (2020), France	Randomized controlled trial, multicenter	149 hospitalized patients with severe COVID-19, the median age was 62 years, 70 % men, 30 % women	Hydrocortisone, 200 mg/day IV for 7 days, then 100 mg/day for 4 days, then 50 mg/day for 3 days	Hydrocortisone did not reduce mortality of acute respiratory failure of patients with COVID-19 compared with controls at day 21 (32/76 (42.1 %) GC vs. 37/73 (50.7 %) placebo). Trial stopped prematurely following information from RECOVERY study.
[176] COVID Steroid 2, Denmark	Randomized controlled trial, multicenter	971 hospitalized patients with severe COVID-19, the median age was 65 years, 69 % men, 31 % women	Dexamethasone 12 mg/day IV up to 10 days	In severe COVID-19, 12 mg/day compared with 6 mg/day of dexamethasone did not result in statistically significantly more days alive without life support at 28 days.
[168], USA	Retrospective observational study, single center	262 adult patients with severe COVID-19, the median age was 61 years, 75 % men, 25 % women	Methylprednisolone dosed at least at 1 mg/kg/day for $\geq$ 3 days (n = 104), or dexamethasone dosed at least at 6 mg for $\geq$ 7 days	GC therapy reduces mortality at day 50 (17/104 (16.4 %) methylprednisolone, 22/83 (26.5 %) dexamethasone, 31/75 (41.3 %) usual care)
[169], Argentina	Randomized controlled trial, multicenter	98 adult COVID-19 patients with ARDS, the median age was 61,5 years, 70 % men, 30 % women	High-dose dexamethasone: 16 mg/day IV for 5 days, then 8 mg/day IV for other 5 days; low-dose dexamethasone: 6 mg/day IV for 10 days	High-dose dexamethasone compared with low-dose dexamethasone did not result in statistically significantly changes in mortality rate at 28 days (19/49 (39 %) low-dose dexamethasone vs. 20/49 (41 %) high-dose dexamethasone).

Abbreviations: ARDS: acute respiratory distress syndrome; GC: glucocorticoid; IC: intensive care; IV: intravenous; MV: mechanical ventilation.

guidelines have been described in detail aimed to define how to manage the disease in case of combination therapies, including integrated chinese and western medicine, especially for old patients, as they are the main focus of the treatment of severe COVID-19 [13–15].

GC are anti-inflammatory and immunosuppressive drugs widely used in many autoimmune and immune mediated inflammatory diseases, such as rheumatoid arthritis (RA), asthma and inflammatory bowel disease (IBD) [16,17]. Most of their therapeutic effects are due to their interaction with different glucocorticoid receptors (GRs), that brings changes of complex molecular mechanisms, mainly involving gene expression and intracellular signaling regulation. This results in the modulation of immune cell activation and action, and in the inhibition the production of many pro-inflammatory cytokines [18].

Evidence related to the use of GCs in COVID-19 deriving from randomized controlled trials, systematic reviews and meta-analyses indicates their efficacy in patients requiring oxygen support (Table 1) [19,20]. On the other end, as expected, patients under chronic therapy with high GCs dose regimens are more susceptible to infections, including SARS-CoV-2 infection and consequent COVID-19 development [21–24]. Importantly, GC use in COVID-19 remains a subject of debate as the time and duration of treatment, phase of the disease and co-morbidities may be important and influence the efficacy and/or the side effects induced by GCs [25].

This review intends to summarize some of the effects of GCs on the major cellular and molecular components of the inflammatory/immune system, their use in common inflammatory and autoimmune diseases, as well as in the management of COVID-19.

2. Anti-inflammatory mechanisms of GCs

It is well known that the endocrine system is involved in the regulation of inflammation and immune response so that the immune-neuroendocrine activity contributes to inflammatory and autoimmune diseases [26,27]. In particular, endogenous GCs are essential for survival as they control many physiological body functions, including inflammation and the stress response [16]. Among the many actions of both endogenous GCs and their structurally homologous drugs is the control of mechanisms involved in cell growth and survival and consequently of tissue integrity [16,18,28]. This GC regulatory activity on cell fate is common to all types of cells and organs in the body, which is consistent with the presence of GRs in all cells, the existence of GR recognition elements in all chromosomes [29,30] and the GR-mediated regulation of gene transcription in a complex system acting as dimers (homo- or hetero-dimers), monomers or tetramers.

The important effects of GCs on inflammation and immune response are due to regulation of cellular components of the immune/inflammatory system, to the regulation of expression and release of soluble factors and expression of their receptors and to the modulation of expression and activity of molecules of the intracellular signaling systems [16–18]. The majority of mechanisms involved in the anti-inflammatory activity of GCs are attributed to the direct modulation of gene transcription, including regulation of genes that control cell activation and production of mediators of inflammation [18]. As an example, GCs influence prostaglandin (PG) synthesis, by interaction with GRs, that are transcription factors, and by transcriptional up-regulation of the glucocorticoid-induced leucine zipper (GILZ), and consequently of Annexin-1, which then counters phospholipase A2 (PLA2) activity and arachidonic acid (a precursor in the synthesis of prostanoids) release, a mechanism also involved in GC-regulated apoptosis [31,32]. Moreover, GCs inhibit the cyclooxygenases (COXs) and consequently the metabolism of arachidonic acid [17,33,34].

GCs also act as anti-proliferative agents and inhibit lymphocyte proliferation and clonal expansion. This immunosuppressive effect is partly achieved by inhibition of immunomodulatory transcription factors, such as the NF-κB and activator protein 1 (AP-1) and by blocking signal transduction MAPK pathways through several mechanisms [16–18,28,35]. The down-regulation of the markers of inflammation, coagulation and fibroproliferation activated by NF-kB [36,37] contributes to the acceleration of the resolution of the disease [36,38,39].

In addition to the GRs direct interaction with components of the MAPK pathway, GCs can also up-regulate GILZ, which then binds to and inhibits different molecules of the MAPK pathway, such as Ras and the extracellular-signal-regulated kinase (ERK) [29,40]. Another example of GC anti-inflammatory activities, mediated by NF-κB, AP-1 and the MAPK pathway, is the inhibition of some cytokine production including IL-6, IFN-γ and TNF [16]. Finally, another important aspect of the GCs anti-inflammatory and immunomodulatory activity is their capability to induce cell death in most of the cells of the immune system, including T and B lymphocytes, monocyte/macrophages and natural killer (NK) cells [17,28]. Interestingly, GCs can also protect T cells from cell death in specific conditions when, at the same time, TCR triggering or other specific signals promote activation and differentiation of T cells.

SARS-CoV-2 infection triggers the immune response and enforces inflammatory molecules production. GCs may control multiple mechanisms of the activity of different immune cells driving both the innate and the adaptive immunity. In particular, GCs inhibit the adaptive immune response by controlling activation, proliferation and survival of T and B lymphocytes. In addition, GCs regulate the expression of adhesion molecules and the production of chemotactic factors, thus modulating T and B cell trafficking in and out of vessels and favoring resolution of tissue specific inflammatory site [16,17].

It is well known that GCs counteract T cell activation, thus contributing to “anergy” and to the inhibition of the immune/inflammatory response. Lymphocyte activation and proliferation, consequently to antigen/T-cell receptor (TCR) interaction, is a pre-requisite for clone expansion and development of the immune response, as well as for the production of soluble and membrane factors, including IL-2 and the consequent Fas-Fas ligand (FasL) over-expression [41]. Based on these mechanisms, GCs modulate T cell selection and the development of the immune/inflammatory response. GCs inhibit lymphocyte activation and proliferation, but also cell death consequent to activation, involved in antigen-triggered T cell clone selection, and render T lymphocytes anergic therefore contributing to the inflammatory/immune response inhibition [42]. Moreover, the effect of GCs on T cell death is also dependent upon the simultaneous stimuli by cytokines in the microenvironment and by co-signals, such as those of cluster of differentiation (CD)28 and CD137 (4–1BB) [43–45]. At the same time, GC/GR interactions regulate T cell differentiation to favor T helper 2 (Th2) and regulatory T (Treg) cell development that, like induction of effectors T cell anergy, can be considered as mechanisms contributing to the anti-inflammatory effect of those drugs [46,47].

Similar immunomodulatory effects are also directed against B lymphocytes that represent an important component of the immune/inflammatory response. Indeed, GCs also inhibit B cell activation, growth and survival as well as dampen antibody production and release of immunomodulatory cytokines [48–50].

Innate immunity also contributes to the inflammatory and immune response against infectious agents and tumors. GC-mediated anti-inflammatory activity is also facilitated by regulation of innate immunity, including the activity of NK cells, macrophages, dendritic cells (DC) and neutrophils. Similar to T and B lymphocytes, GCs inhibit pro-inflammatory cytokines in cells of the innate immunity, including IL-6, IL-1β, IL-17, IL-12, GM-CSF, and TNF. Notably, COX-2, PGs and the inducible nitric oxide synthase (iNOS) are also reduced by GCs [17,51].

Interestingly, depending on the conditions, stress-induced GCs signals could also produce a pro-inflammatory effect beside the anti-inflammatory ones. For instance, systemic exposure to exogenous GCs has been reported to potentiate the pro-inflammatory response to lipopolysaccharide (LPS) in peripheral macrophages and may increase production of mediators of inflammation such as pro-inflammatory cytokines [52,53]. The GC pro-inflammatory effects seem to be relevant particularly in neuroinflammation, and GC activities induced by chronic

stress are associated with increased expression of the pro-inflammatory cytokines IL-1β and TNF [54] and with long-term or chronic pathological conditions in the brain [55–57].

NK cells exhibit cytotoxic activity and are classified among the recently described innate lymphoid cell (ILC) subsets. In particular, NK cells are relevant in the response against tumors and infections and play an important role in many inflammatory and autoimmune diseases, such as RA, systemic lupus erythematosus (SLE) and diabetes. Moreover, they elicit regulatory roles and influence both the innate and adaptive immunity by producing and releasing different cytokines that, in turn, can regulate NK cell activities. GCs, through genetic and epigenetic mechanisms, inhibit NK cell cytotoxic activity by, at least in part, decreasing production of granule constituents such as granzyme-B and perforins. In addition, GCs can modulate NK cell production of pro-inflammatory cytokines, including IL-6, IFN-γ and TNF, and NK cell migration by inhibition of lymphocyte function-associated antigen (LFA)-1 expression [58–60]. For instance, GCs reduce the production of cytokines such as IFN-γ by NK cells, thus conferring protection against damage and the disease mediated by pro-inflammatory cytokines. Finally, GC-induced PD-1 expression on NK cells has been recently described as an important factor for survival during infections [61,62].

Anti-inflammatory GC effects also comprise the control of macrophages activity, which is another important component of innate immunity. In particular, GC treatment inhibits the generation of inflammatory mediators and increases phagocytosis, thus contributing to their anti-inflammatory effect [51]. Administration of high doses of GCs inhibits several pathways, including MAPK signaling, AP-1 and NF-κB transcription activity in macrophages/monocytes and the subsequent production of pro-inflammatory cytokines, such as IL-1 and IFN-γ [63]. GCs also favor macrophage differentiation, switching to an anti-inflammatory phenotype that can contribute to the process of resolution of inflammation. This effect is further enhanced by the GC anti-apoptotic effect on macrophages. The GC-induced increased macrophage survival may also contribute to the innate immunity-mediated resistance against microbial infections [17].

GCs also exert anti-inflammatory effects by modulating neutrophils functions. Notably, the effects of GCs are very complex and can result either in activation or inhibition of the inflammatory activity mediated by neutrophils. Similar to T lymphocytes, GCs inhibit neutrophil activation, but at the same time they increase their survival, that could contribute to the increase of circulating neutrophils caused by GC treatment. Furthermore, GCs modulate leukotriene (LT) production and expression of IL-1 receptors [64]. GCs can favor resolution of inflammation by modulating intracellular signaling pathways, including MAPK and p38 cascades, and by GC-mediated up-regulation of GILZ and Anxa-1 gene expression and by modulation of Bcl-2 family expression [39].

GCs can also inhibit neutrophil adhesion and migration by reducing the expression of L-selectin in neutrophils along with the GC-induced inhibition of adhesion molecules expression in endothelial cells. As neutrophils adhesion, rolling and blood exit to inflammation sites are essential for the inflammatory process, this may well contribute to the anti-inflammatory actions of GCs [65,66].

Dendritic cells (DC) are important antigen-presenting cells (APC) that regulate T cells activation and generation of memory T lymphocytes. Their antigen-presenting function is increased by DC maturation that is under the control of different stimuli, including cytokines. After GC/GR interaction there can be a reduction of DCs that can also be rendered “tolerogenic”, thus losing their promoting and immune-stimulating action on inflammatory/immune processes [51,64]. GCs can act on DC cells through various mechanisms including up-regulation of GILZ and consequent inhibition of maturation, increase of apoptosis, inhibition of pro-inflammatory cytokines and increase of cytokines such as IL-10 and transforming growth factor (TGF)-β; all these effects contribute to the anti-inflammatory activity of GCs [67,68].

Another important aspect is the spare or enhancing effect of GCs on various innate immunity effectors, including complement, collectins, acute-phase proteins and secretory leukocyte protease inhibitor (SLPI), produced by respiratory epithelial cells, that can contribute to antimicrobial defense [69]. These effects, together with the increased neutrophil and macrophage actions, can contribute to the GC-induced increase of innate immune activity and resistance against infections.

The actions of GCs on the aforementioned cells are summarized in Fig. 1.

3. Use of GCs in inflammatory diseases

The first GC successfully used in the treatment of human inflammatory conditions was cortisone, employed in 1948 to treat RA patients by Philip Hench in Mayo Clinic [70,71]. For more than 70 years, the immunosuppressive function of GCs proved to be a powerful tool in preventing rejection of organ transplants and in chronic inflammatory conditions such as asthma, allergies, chronic obstructive pulmonary disease (COPD), RA, SLE, IBD, multiple sclerosis (MS) and malignancies [17,72–74]. Over the years, numerous synthetic steroids with anti-inflammatory properties have been developed and used for their beneficial effects in human pathology. Indeed, GCs are unquestionably among the most prescribed classes of drugs, with widely documented efficacy [75,76].

3.1. GCs and the circadian clock

The release of endogenous CGs is regulated by the circadian clock in accordance with energy-demanding situations. This derives from the observation that in humans, GCs are mainly released in the early morning hours [77]. Furthermore, the interplay between the hypothalamic-pituitary-adrenal (HPA) axis and the immune system might influence GCs release as well. It has been indeed suggested that late night administration of GCs is more effective than early morning administration, since the immune system typically starts to be activated after midnight and peaks early in the morning. This immune activation increases in some inflammatory conditions, such as RA, gout, or allergic asthma, and cannot be controlled by endogenous GCs, since their production is inadequate due to chronic inflammation and the consequent downregulation of the HPA axis. Therefore, administration of exogenous GCs during nighttime ameliorates morning symptoms in RA patients [78].

The effects of GCs normally require time to take place, mainly due to GC acting at a genomic level on gene expression. However, there have been reports of some faster effects of GCs, prompting the concept of non-genomic functions of GCs which might also influence the course of inflammatory diseases. For example, GCs can enhance the effects of bronchodilators in a short time frame [79]. However, the mechanisms at the basis of these faster effects require further investigations.

3.2. Adverse events of GCs

Despite their beneficial actions, there have been reports of severe adverse events linked to long-term administration of GCs involving the gastrointestinal, cardiovascular, endocrine, nervous, ocular and immune systems [80]. Several efforts aimed at reducing the adverse effects were attempted, in order to avoid the burden of additional drugs for the patients or the suspension of the treatment. Unfortunately, most of these efforts were unsuccessful. Some of these approaches included the development of new molecules and formulations or modifications of the existing compounds. For instance, in asthma, the topical administration of GCs has succeeded to at least partially resolve the adverse effects of systemic GC therapy. In addition, patients receiving long-term treatments with GCs have been reported to develop adrenal insufficiency (e.g. around 37 % of RA patients). This was due to negative feedback regulation of GC production, which inhibits the HPA axis, its function requiring some time to be restored [81].

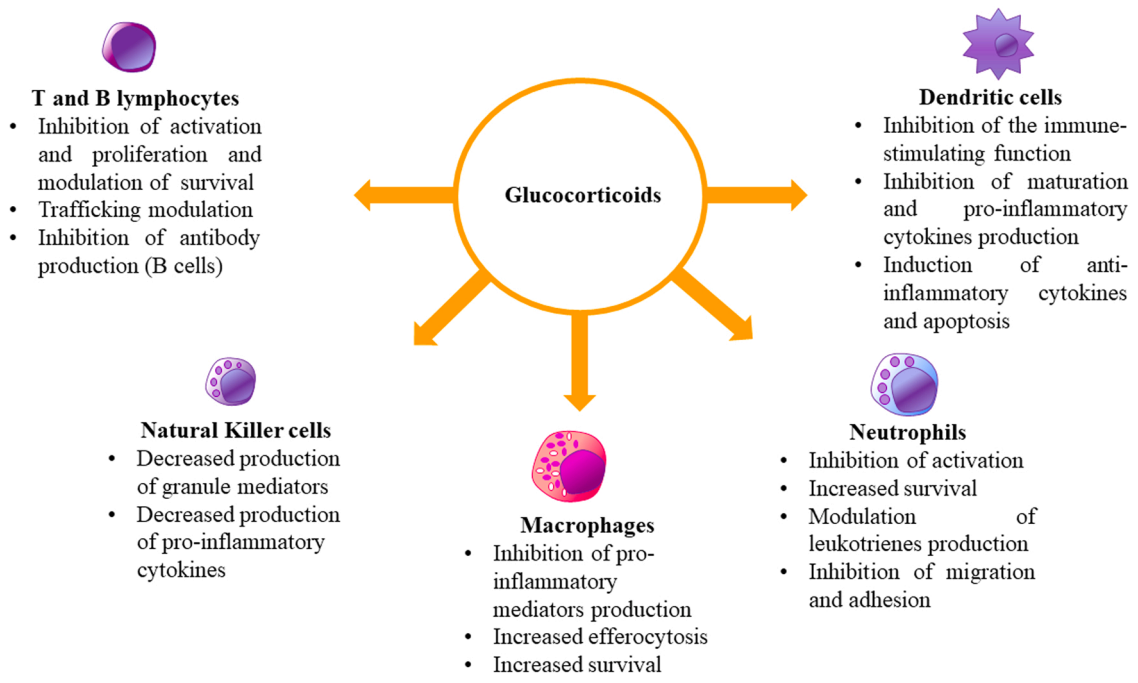

Fig. 1. Glucocorticoid effects on cells of the immune system.

Treatment with GCs is not always effective, due to the development of resistance to their effects. After being first described in the 1970s in vitro, GC resistance has been reported mostly in asthma and RA, with 4–10 % and 30 % of the patients not responding to treatments, respectively [82]. Almost complete resistance to GCs has been seen in COPD [83]. The mechanisms accounted for GC resistance range from individual genetic variations to molecular alterations of GC receptors [17, 83].

Regarding the topical use of GCs, the loss of their efficacy over time commonly referred to as tolerance or tachyphylaxis is not fully characterized [84].

3.3. *Use of GCs in respiratory diseases and acute lung injury (ALI)*

GCs are currently employed in treating several types of inflammatory lung disorders, although their efficacy is not always guaranteed. Among lung inflammatory diseases, asthma and COPD occupy a special place because of their high frequency (more than 500 million people worldwide affected) [85]. Asthma is a respiratory disease caused by hyperresponsiveness of the airways to environmental factors and commonly manifested by cough, dyspnea, and/or wheezing [86]. Asthma can be classified in various types based on the different underlying pathologic mechanisms and immune cells involved. Therefore, the disease shows high degree of heterogeneity with the main types being the allergic and neutrophilic asthma [87–89]. The allergic type is the most common, and characterized by high serum levels of immunoglobulin E (IgE), infiltration of eosinophils into the lung, degranulation of mast cells, and release of inflammatory cytokines such as IL-4, IL-5, and IL-13 [86,90]. The neutrophilic endotype is principally linked to Th17 cells, with increased expression of pro-neutrophilic factors, such as IL-8, IL-1β, and IL-6, possibly indicating the presence of underlying infections [86,90]. GCs are mainly employed in the management of allergic asthma, while neutrophilic asthma does not seem to respond effectively to GCs [91].

COPD etiology lies in inhaled irritants, such as tobacco smoke. These compounds lead to airways remodeling, resulting in impaired airflow and chronic bronchitis [92]. GCs use in COPD remains controversial, as a number of studies show that COPD patients are not responsive to GCs [93,94]. These differences might be explained by the effects of GCs on cell death, such as the reported apoptosis induction in eosinophils and impairment in neutrophils [64,95]. It is noteworthy that allergic asthma might display GC resistance, yet the underlying mechanisms are still poorly understood. Blockade of GC translocation to the nucleus via p38-induced phosphorylation of the GC receptor has been suggested as a putative mechanism involved in GC resistance [96].

ALI and its severe form ARDS are inflammatory disorders that can result from severe trauma or sepsis and involve hypoxemia, pulmonary edema, and leukocyte infiltration [97,98]. Mortality due to ALI is extremely high, possibly exceeding 40 % [99]. ALI is characterized by loss of the integrity of the endothelial–epithelial barrier in the alveoli and by increased production of pro-inflammatory mediators, leading to leukocytes recruitment, predominantly neutrophils [99,100]. Strategies employed to treat ALI mostly involve supportive care practices, but there is evidence that GCs might be of use in ALI [101]. However, their effectiveness is still controversial [102–104]. As a result, there is not definitive recommendation of GCs in the therapy of ALI.

3.4. *Use of GCs in (auto)immune and (auto)inflammatory disorders*

Since their first use to treat RA in 1948, GCs remain the mainstay in the management of (auto)immune and (auto)inflammatory disorders [71]. RA is an autoimmune disease with global prevalence estimate of 0.46 %, with variations due to geographical location and study methodology [105]. The main feature of RA is persistent synovial inflammation, which leads to damages in the joints, cartilages and bones. Moreover, in RA patients T and B cells acquire a primed status and begin to produce autoantibodies [106]. Together with the production of pro-inflammatory mediators, these processes are responsible for the activation of synovial fibroblasts and macrophages, ultimately leading to an exacerbated inflammatory response. Although there are several medications for the treatment of RA, such as NSAIDs, disease-modifying anti-rheumatic drugs (DMARDs), and biologics, GCs remain the golden standard in the clinical management of RA.

GCs are also used in the treatment of SLE. Innate and adaptive immune system are activated by self-antigens in SLE resulting in the production of autoantibodies, complement activation, cytokine production and consequent damage of multiple organs, such as skin, kidney, joints, lung and blood counts [107]. The management of SLE aims at the treatment of flares and disease symptoms and consists of combinations

of hydroxychloroquine (HCQ), GCs at a recommended daily dose of $\leq$ 7.5 mg prednisone equivalent [108], immunosuppressive drugs, such as azathioprine, methotrexate, mycophenolate mofetil and biologics, such as belimumab [108,109].

Similarly, the anti-inflammatory actions of GCs are utilized to manage Crohn's disease (CD) and ulcerative colitis (UC). Notably, genetic and environmental factors, the gut microbiome and both the innate and adaptive immune system contribute to the pathogenesis of IBD [110]. The most commonly used first-generation GCs are prednisone, methylprednisolone, and hydrocortisone to alleviate the clinical symptoms. However, long-term therapy with first-generation GCs results in significant adverse effects. These can be ameliorated by the use of second-generation GCs, such as budesonide and beclomethasone dipropionate (BDP), which combine high anti-inflammatory capacity and decreased bioavailability [73].

Finally, GCs are the main drugs used to manage multiple sclerosis (MS) relapses. MS is an inflammatory disease of the central nervous system (CNS) [111]. The relapse is the most obvious clinical manifestation of MS corresponding to a focal or multifocal, acute or subacute CNS demyelinating inflammation [112]. The treatment of MS relapse consists of GCs, adrenocorticotropic hormone (ACTH), and plasma exchange [113]. The dosage, route of administration, type and length of time of GC administration are variable [113]. As an example, methylprednisolone, first approved in 1951 [114], reduces the inflammatory immune response, decreases CD4 lymphocyte count and inhibits T cell activation. In addition, methylprednisolone reduces the migration of immune cells from the peripheral blood into the CNS [115].

4. Inflammation and COVID-19

The severity and prognosis of COVID-19 strongly correlates with the degree of the inflammatory response. SARS-CoV-2 induces inflammation from the initial phase of viral invasion. When the immune system is unable to fight against the virus, pulmonary and systemic hyperinflammation follows [116]. Following binding of the viral S protein to the ACE2 receptor that is mostly expressed in pneumocytes type II and ciliated bronchial epithelial cells [116], the virus enters into the target cells and the cytopathic SARS-CoV-2 replicates releasing damage-associated molecular pattern proteins (DAMPs) and pathogen–associated molecular pattern proteins (PAMPs). These are recognized by pattern recognition receptors (PRRs) resulting in innate immunity activation [117,118]. Infected cells carry PAMPs and uninfected but damaged cells produce DAMPs; both of them trigger inflammation. The inability of the innate immune system to clear the aforementioned cells and molecular patterns constitutes a fundamental factor for hyperinflammation and increased COVID-19 severity. Additionally, the decreased type-I IFN response and the increased activation and recruitment rate of innate immune cells strongly predispose to an hyperinflammatory state [119]. Interestingly, related studies suggest that the S protein decreases ACE2 regulation inhibiting the renin angiotensin system (RAS) and intensifying inflammation and vascular permeability [120].

A balanced immune response against SARS-CoV-2 contributes to the successful eradication of the virus in the majority of patients. However, an inadequate immune response leads 10–15 % of COVID-19 patients to suffer from a severe dysregulated inflammatory response and a cytokine storm [116], characterized by the dysregulated activation of cytokines by the innate immune system due to ineffective viral clearance, inadequate levels of type I interferons (IFN-I), increased neutrophil extracellular traps (NETS) and other miscellaneous mechanisms [121,122]. The massive cytokine production results in increased inflammatory markers including procalcitonin, ferritin, C-reactive protein (CRP), IL-2 receptor (IL-2R), IL-6, IL-8, IL-10, TNF-α, lactate dehydrogenase (LDH), and low levels of B, T and NK cells. Clinically, in patients with COVID-19, the cytokine storm commonly refers to the condition characterized by elevated levels of TNF, IL-1, IL-10 and IL-6 [3,12]. In any case, the final outcome is the predisposition to organ dysfunction such as ARDS and heart, liver, kidney or multiple organ failure [118,122].

After recognition of viral RNA as PAMPs by PRRs, such as the toll-like receptors (TLR) 7 and 8, the transcription factors interferon regulatory factor (IRF)3/7 and NF-κB are upregulated, increasing in turn the expression and release of IFN-I and pro-inflammatory cytokines, respectively. However, in patients with severe COVID-19, the IFN-I response seems to be reduced or delayed due to the inhibitory role of SARS-CoV-2 proteins, such as M protein, and decreased production of IFN-1 by the decreased plasmacytoid dendritic cells (pDCs) [123]. The protective role of IFN-I in innate immunity is also confirmed by the critical pneumonia caused by inborn errors of TLR3 and IRF7-dependent IFN-I activation [124].

In addition, the recognition of high mobility group box 1 protein (HMGB1), S100, mitochondrial DNA [125] and other types of DAMPs induces IL-6 release and inflammasome activation. The inflammasome NLRP3 is the most common type and results in production of IL-1b and gasdermin D, both favoring a prothrombotic state [117,126]. The NLRP3 inflammasome causes inflammatory cell death through pyroptosis and further immune cell activation [125,127]. It is important to highlight that DAMP molecules play a major role in COVID-19 hyperinflammation, as they generate positive feedback between tissue destruction and innate immune system activation. The continuous release of DAMPs due to tissue hypoxia and ischemia results in an inflammatory and coagulative cycle. The DAMPs act on neutrophils to produce NETs promoting hypercoagulation and impaired endothelial function [125]. The novel SARS-CoV-2 impairs endothelial function and coagulation dysregulating platelets, neutrophils and endothelial cells. The result is the formation of microvascular thrombi containing neutrophils and platelets in the surface of pulmonary endothelial cells. This phenomenon is known as immuno-thrombosis [117,128].

The inflammatory signaling cascades of the cytokine storm include IL-6/JAK/signal transducer and activator of transcription (STAT), IFN-γ/JAK/STAT, TNF-α/NF-κB, NLRP3/IL-1β, IL-2/IL-2R/JAK/STAT5, IL-7/IL-7R, IL-10, IL-12, IL-17 and GM-CSF signaling [123]. IL-6, which is characteristically elevated in severe COVID-19 patients, activates the NF-κB and JAK/STAT3 pathways. The hyperactivation of the NF-κB and STAT3 inflammatory pathways induces the IL-6 amplifier (IL-6 AMP) leading to an enhanced NF-κB activation. The overactivation of NF- κB results in ARDS, multi-organ failure and coagulation [129]. As a result, high levels of IL-6 cause hyperinflammation, endothelial dysfunction and cytokine storm [130]. The intensified inflammatory cell activation and the subsequent secretion of reactive oxygen species (ROS) and proteases result in diffuse alveolar damage, ARDs, inefficient gas exchange and hypoxia. Beyond lung epithelial and vascular cells, the massive cytokine storm, followed by the increased levels of TNF, can damage the entire organism by inducing septic shock and multi-organ failure [131].

The cytokine storm in SARS-CoV-2 infection may also be stimulated by the lectin, classical and alternative pathways of complement cascade. The increased C3a and C5a anaphylatoxins promote a massive inflammation. In addition, the complement cascade activates the hemostatic mechanisms leading to endothelitis and thrombotic lesions; conditions that found in severely ill COVID-19 patients [116]. It should be noted that the cytokine storm induced by SARS-CoV-2 resembles that caused by bacterial sepsis. The use of GCs in sepsis is controversial due to the suppression of immune system creating concern in their use in COVID-19 [62]. However, the high mortality rate of COVID-19 patients due to cytokine storm and the consequent ARDS/ALI highlights the use of GCs to combat the hyperinflammation [132].

The management of cytokine storm is based on the inhibition of pro-inflammatory factors, such as IL-6 and the activation of anti-inflammatory factors, such as IL-10. GCs play a significant role in targeting the anti-inflammatory mechanisms, as according to the Randomized Evaluation of COVID-19 Therapy (RECOVERY) clinical trial GCs and specifically dexamethasone are able to regulate satiated or

CD11 blow macrophages. The anti-inflammatory factors IL-10, PGE2, and platelet-activating factor (PAF) are increased by pro-resolving macrophages [19,133,134]. Interestingly, with or without transcriptional mechanisms, the GCs result in decreased expression of genes implicated in inflammatory pathways, like in TLR7 signaling in B-cells, decreased antigen presentation in DCs, elevation of IL-10 levels and decrease of inflammation inducing factors, such as IL-6, TNF-α and PGE2 [134,135].

It is important to highlight that inflammation induces cell death and phagocytosis. The anti-inflammatory role of GCs results in decreased clearance of infected cells and bystander cells demonstrating a negative or positive effect in mild cases. As a result, the net effect on disease severity in mild cases is unknown. However, in severe cases the GCs act on the inefficient cells of innate immunity resulting in a positive net effect [119].

5. GC treatment for COVID-19

GCs represent a low-cost therapy, globally available and easily accessible to all. GCs are among the drugs that continue to be evaluated for the management of COVID-19, due to their anti-inflammatory and immunosuppressive efficacy, as detailed in Section 2. Furthermore, GCs are widely used in the treatment of other diseases closely related to COVID-19, such as severe acute respiratory syndrome (SARS) and Middle Eastern respiratory syndrome (MERS) [136–139].

In severe cases, COVID-19 can result in clinical manifestations such as ARDS and macrophage activation syndrome (MAS), possibly associated with immune-dysfunctions and uncontrolled release of proinflammatory mediators, hypoxic respiratory failure and ultimately death [1,2]. To counteract the excessive inflammation, the use of GC acting at different levels of the inflammatory responses has been proposed

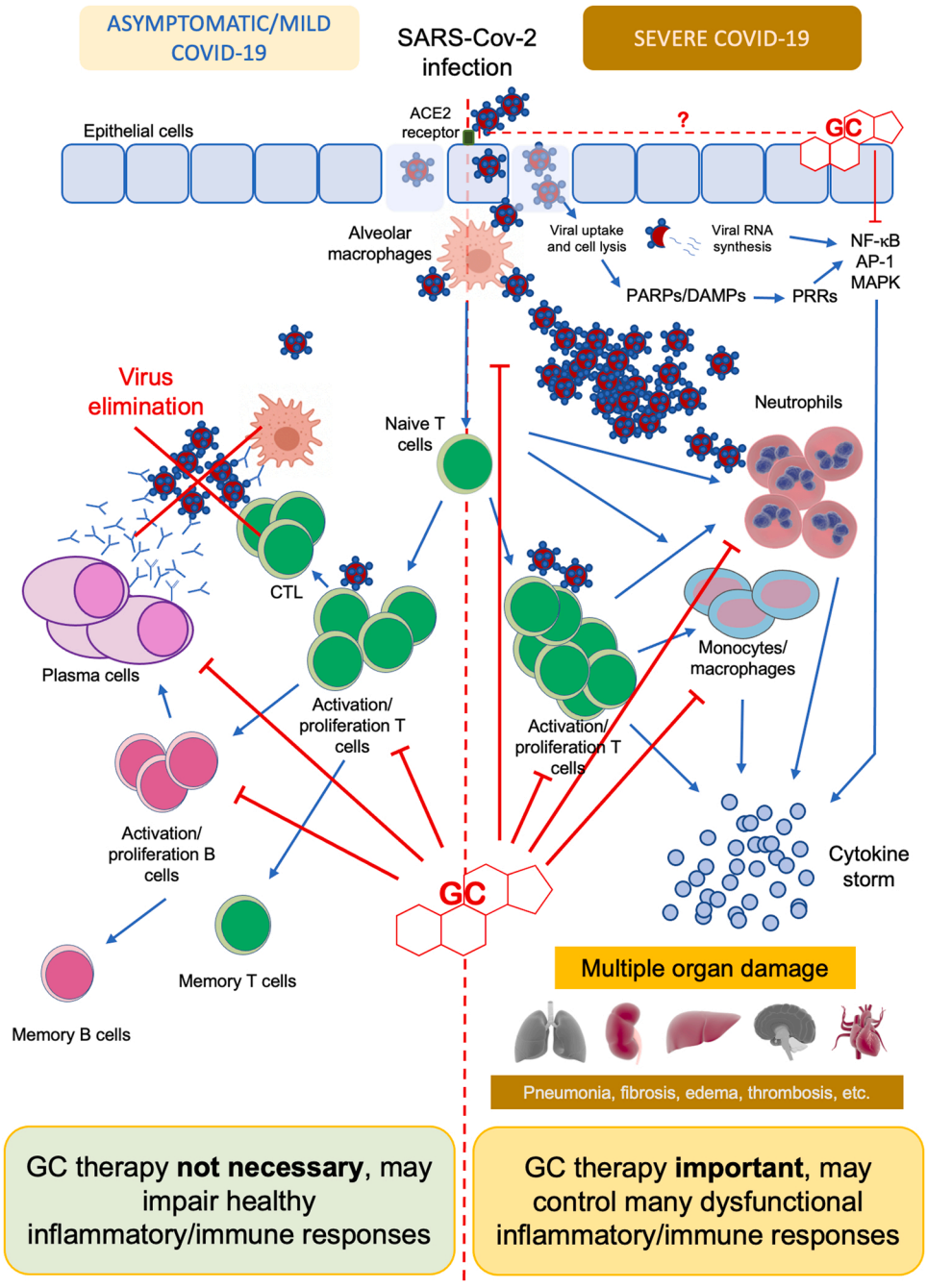

Fig. 2. Schematic representation of pathological events during SARS-CoV-2 infection and efficacy of glucocorticoids (GCs) to control COVID-19 clinical outcomes. Severe acute respiratory syndrome coronavirus (SARS-CoV-2) infects airway cells by binding to angiotensin converting enzyme 2 (ACE2) receptor, leading to cellular and tissue damage and production of damage-associated molecular patterns (DAMPs) by virus-infected epithelial cells as well as of pathogen-associated molecular patterns (PAMPs) of the virus itself. These molecules can interact with pattern recognition receptors (PRRs) expressed on pulmonary epithelial cells and promotes the transcription of several inflammatory cytokine-related genes through proinflammatory pathways such as the NF-κB, AP-1 and MAPK signaling pathways. On the left part of the figure the normal immunological response to SARS-CoV-2 infection is presented, whereas on the right part is illustrated the pathogenesis of severe COVID-19 and the anti-inflammatory/immunosuppressive effects of GCs are illustrated. Abbreviation: ACE2, Angiotensin converting enzyme 2; AP-1, activator protein-1; CTL, cytotoxic T-lymphocyte; DAMPs, damage-associated molecular patterns; GC, Glucocorticoid; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor of κ-light chain of enhancer-activated B cells; PAMPs, pathogen-associated molecular patterns; PRR, pattern recognition receptor.

(Fig. 2).

In the initial phase of the pandemic, in the absence of reliable data from large-scale randomized clinical trials, there was great initial uncertainty about the effectiveness and the risk/benefit ratio of GC therapy in COVID-19. Many treatment guidelines did not initially recommend routine use, unless patients were in refractory shock or were on chronic GC therapy prior to the diagnosis of COVID-19 [24,140–142].

After positive evidences in small studies that included GC treatment in COVID-19 patients, in September 2020 the WHO expressed its favorable opinion suggesting the use of GCs in patients with "critical" COVID-19 [143], manifested by ARDS, sepsis, septic shock or other conditions that required supports such as invasive or non-invasive mechanical ventilation or vasopressor therapy [11]. GC use was also indicated for patients with "severe" COVID-19, where severity referred to the presence of clinical signs of a respiratory rate > 30 acts/min or with pneumonia with oxygen saturation < 90 % in ambient air [143].

In the same period, other international and national regulatory authorities, including the European Medicines Agency (EMA) and the National Institutes of Health (NIH), also gave favorable opinion to the use of GCs in severe COVID-19 patients that required oxygen therapy with or without invasive or non-invasive mechanical ventilation. It should be noted that the guidelines report also a “conditional recommendation” to the non-use of GC therapy in patients with non-severe forms of COVID-19 regardless of hospitalization, but especially in the phase of the most intense viral replication.

In the meantime, several clinical data were collected, and multiple large-scale randomized trials were proposed (Table 1). The most convincing data regarding the use of GCs in COVID-19 patients are those of the RECOVERY trial, published in February 2021, in which more than 6000 patients were involved and where a group of them received 6 mg of dexamethasone for 10 days [19]. This study demonstrated that dexamethasone treatment was beneficial in patients with severe COVID-19 compared to the control group (rate ratio, 29.3 % vs. 41.4 %), but had no significant effects in patients who did not require oxygen mechanical ventilation support (23.3 % vs. 26.2 %) [19].

Other clinical trials confirmed the results of the RECOVERY trials [144–147], including the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) group that performed a meta-analysis of 7 clinical trials in critically ill COVID-19 patients (for a total of 1703 patients), that had as primary objective to estimate the association between GC administration, compared to standard of care, and 28-day all-cause mortality in critically ill patients with suspected or confirmed COVID-19 [148]. This study demonstrated that administration of systemic GCs in severe COVID-19 patients (with sepsis, ARDS, septic shock or signs of severe respiratory distress requiring invasive or non-invasive mechanical ventilation) is associated with lower all-cause mortality at 28 days, compared to standard therapy, without an increased risk of major adverse events [148].

There is still no evidence on the safety and efficacy of GCs in the treatment of patients with early-stage COVID-19 and of those who are not hospitalized. However, many clinical studies indicate that if the treatment starts too early, in the absence of serious symptoms, or too late, in patients with multi-organ failure, there is no benefit or even a worst outcome is expected (Fig. 2) [20,149,150]. A meta-analysis of more of 20,000 COVID-19 patients showed that the overall mortality of COVID-19 patients receiving GCs was higher than of patients not receiving them [151]. Even data from RECOVERY trial suggest a possible harm of GC therapy in patients not requiring mechanical ventilation [19].

Another important concern about the use of GCs that remains to be evaluated, is the possibility of the onset of adverse effects during short-term GC therapy (7–10 days as recommended for COVID-19 treatment). On the other side, prolonged treatment with GC (more than 10 days) might be useful to control post-disease complications, such as pulmonary fibrosis, especially in patients with persisting respiratory distress [152]. However, GC therapy against COVID-19 has also been a subject of controversy and must be used wisely.

A long GC therapy might contribute to the "long-COVID-19 syndrome", which is manifested by fatigue and psychological symptoms, and some post-COVID-19 patients display adverse reactions to GCs such as neuromuscular weakness and neuropsychiatric disorders [17,153]. It is important also to consider the thrombotic complications with long lasting GC use, which can contribute to a poor outcome enhancing the pro-coagulant conditions of patients with COVID-19 [149,154].

The beneficial effect of GCs in severe viral respiratory infections is likely to depend on the timing of administration, dosage and patient type [135,155,156]. As in many other therapeutic applications, dosage and duration of GC treatment are largely empiric. An important issue about the heterogeneity of the GC response is whether variations in the endogenous GC-GR interaction (or in the HPA axis) can contribute to the response in COVID-19 patients. Some authors suggest that COVID-19 patients with pre-existing HPA axis dysfunction should still be considered potentially vulnerable groups [157–159]. Also, patients with adrenocortical carcinoma could be more susceptible to SARS-CoV-2 infection due to the immunosuppressive state caused by unbalanced GC secretion [160].

As aforementioned in Section 3.2, GC resistance may often be another cause of variability in the GC response and/or in the appearance of side effects during the treatment of inflammatory diseases. The impact of genetic variations in GRs on GC actions has been evaluated in many studies [161–163]. However, it is yet unclear whether GR mutations affect GC response in COVID-19 patients. In the context of severe COVID-19 treatment, when patients require oxygen, a potential cause of variability in GC efficacy could be due to hypoxia that leads to a destruction of the anti-inflammatory actions of GCs [164]. Moreover, there is strong evidence that the effects of SARS-Cov-2 are not limited to the respiratory system, and that the disease may involve a wide range of organs. As an example, COVID-19 disease has a lot of overlap with polymicrobial sepsis, a disease in which GC resistance is a major obstacle. Besides recent trials with GCs in sepsis patients, recent studies in animals have shown that severe sepsis leads to a total lack of response to GCs, and that this can be due to a major metabolic impairment, namely the lack of gluconeogenesis in hepatocytes, leading to accumulation of lactate, alanine and other gluconeogenic substrates [165]. Furthermore, SARS-Cov-2 infection may predispose patients to diabetes [166]. More studies on COVID-19–related metabolic diseases are warranted, also to uncover novel mechanisms of the disease that may impact GC therapy.

Even the comparison between different types of GCs is very difficult because most of the data are collected from small size clinical trials. More randomized controlled trials with larger sample sizes and different follow-ups are required to evaluate the beneficial effect of one GC compared to the others. The data from the different clinical studies mainly concerning dexamethasone and hydrocortisone, and to a lesser extent methylprednisolone, do not allow to place a preferential indication to one active ingredient over another. Moreover, at present there are no data showing a greater efficacy of high doses than reduced doses [144,167–169]. As indicated by the RECOVERY trial [19], for dexamethasone the recommended dosage in adults and adolescents is 6 mg once daily for up to 10 days. In the REACT study, together with the RECOVERY trial, different GCs were used with different dosages in the different studies were described: 20 mg/day for 5 days then 10 mg/day for another 5 days of the Dexa-Covid19 trial, 200 mg/day of hydrocortisone for 4 days then 100 mg for 2 days, 50 mg/day for 2 days of the Cape-Covid trial, 40 mg every 12 h of 6-methylprednisolone for 5 days of the Steroids-SARI trial [148]. Another study indicated that methylprednisolone treatment vs. dexamethasone has a better outcome for hospitalized COVID-19 patients. The authors of this study suggested that methylprednisolone may be more effective for lung injury compared to dexamethasone [168]. The use of non-comparable dosages between active molecules with different pharmacodynamic and pharmacokinetic characteristics is an important bias. However, NIH and other regulatory

authority guidelines for the COVID-19 treatment indicate GC equivalent dosages referred to 6 mg/day for dexamethasone, as 32 mg/day for methylprednisolone, 40 mg/day for prednisone and 160 mg/day for hydrocortisone. Administration can be both oral and intravenous but, taking into account a possible reduction in absorption in the critically ill patient, the latter modality would be preferable.

The scientific community dedicated particular interest also to inhaled GCs. A recent randomized trial showed that administration of 800 μg/die budesonide in COVID-19 patients at home reduced the risk of hospitalization and time to recovery compared to patients treated with standard paracetamol-based therapy or other NSAIDs, such as ibuprofen or acetylsalicylic acid [170]. Another study reports that inhaled GCs reduce the expression of the SARS-CoV-2 entry receptor ACE2 in human airway epithelial cell cultures and in vivo in mouse models [171]. However, EMA's COVID-19 taskforce (COVID-ETF) suggests that there are still insufficient data on use of inhaled GCs (i.e. beclomethasone dipropionate, budesonide) to treat COVID-19.

There are still many doubts on whether there is any difference in the efficacy of different GCs (i.e. prednisone vs. dexamethasone) in COVID-19 patients. Biochemical and physiological biomarkers, such as cytokines, respiratory parameters, and radiological evidence should be optimally and efficiently combined to tailor GC treatments to COVID-19 patients.

6. Conclusions

GCs modulate most of the cell and soluble components of inflammation. Those effects are in part due to direct and indirect regulation of gene transcription, activity of other transcription factors, and intracellular signaling responsible for inflammation. Moreover, GC-mediated epigenetic mechanisms can contribute to long lasting effects. The GC capability to counter immune/inflammatory cells activation and pro-inflammatory soluble factors release, as in many inflammatory pathologies, could represent in certain clinical conditions an appropriate therapeutic approach to COVID-19 patients (Fig. 2). Notably, recent data have shown that GCs are efficient in severely ill patients infected with SARS-CoV-2, yet without reducing the risk of mortality, hospitalization length and duration of viral elimination [121,172]. Consequently, systemic GCs are limited to severe complications of COVID-19, including ARDS, and are not indicated routinely.

CRediT authorship contribution statement

Stefano Bruscoli: Conceptualization, Writing – original draft, Visualization, Writing – review & editing. **Pier Giorgio Puzzovio:** Visualization, Writing – original draft. **Maria Zaimi**: Writing – original draft, Writing – review & editing. **Katerina Tiligada:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Francesca Levi-Schaffer**: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Carlo Riccardi:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declarations of interest

None.

Data Availability

No data was used for the research described in the article.

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