ISSN print 2414-4517, ISSN online 2710-1487, https://ecm.knmu.edu.ua, ecm.journal@knmu.edu.ua

Infectious and Parasitic Diseases

UDC: 616.9:615.21/.26

ASPECTS OF PHARMACOTHERAPY WITH STEROIDS IN SARS-CoV-2 INFECTION (literature review)

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In recent years, the SARS-CoV-2 pandemic has posed a significant challenge to global public health. Furthermore, infection with SARS-CoV-2 can result in acute respiratory distress syndrome due to excessive systemic inflammation, leading to multiple organ failure and eventual death. Furthermore, the challenge of reducing excessive systemic inflammation, specifically by decreasing the production of pro-inflammatory cytokines in response to SARS-CoV-2, remains unresolved. The use of glucocorticosteroids for SARS-CoV-2 infection remains controversial. Further research is required to support the routine use of steroids in intensive care protocols for SARS-CoV-2, as the current basis is insufficient. This review provides an analysis of literary sources, guidelines, and modern international recommendations on pathogenetic therapy of SARS-CoV-2 to prevent and eliminate hyperproduction of pro-inflammatory cytokines using glucocorticosteroid agents. The aim of this work is to analyse contemporary literary sources on the clinical and pharmacological justification for the use of glucocorticosteroids in clinical practice for SARS-CoV-2 infection. The scientific literature analysis indicates that glucocorticosteroid therapy cannot be recommended for routine use in therapeutic practice for patients with SARS-CoV-2 infection. Thus, with a mild course of SARS-CoV-2 infection, when the patient does not need oxygen support, glucocorticosteroids are contraindicated. Whereas in severe course, in acute respiratory distress syndrome with severe respiratory failure, their use is absolutely necessary, and they are recommended for mandatory use. There is a need for a generalised definition of the optimal glucocorticosteroid agent, including indications, dosage, and duration of use in SARS-CoV-2 infection therapy programs.

Keywords: *systemic inflammatory reaction, proinflammatory cytokines, hypothalamic-pituitary-adrenal system, glucocorticosteroids.*

	Цитуйте українською: Моісєєва НВ, Власова ОВ, Мягкохліб АА. Аспекти фармакотерапії стероїдами при SARS-CoV-2 інфекції (огляд літератури). Експериментальна і клінічна медицина. 2024;93(1):25-33. https://doi.org/10.35339/ekm.2024.93.1.mvm [англійською].
	Cite in English: Moisieieva NV, Vlasova OV, Miahkokhlib AA. Aspects of pharmacotherapy with steroids in SARS-CoV-2 infection (literature review). Experimental and Clinical Medicine. 2024;93(1):25-33. https://doi.org/10.35339/ekm.2024.93.1.mvm

ISSN print 2414-4517, ISSN online 2710-1487, https://ecm.knmu.edu.ua, ecm.journal@knmu.edu.ua

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It is now established that infection with SARS-CoV-2 leads to acute respiratory distress syndrome, which causes severe hypoxia and pulmonary edema. This can quickly result in multiple organ failure and ultimately death [1]. Furthermore, literary sources indicate that the mortality of patients in Intensive Care Units (ICU) worldwide, is as high as 60%, despite the use of etiotropic and pathogenetic anti-inflammatory anticytokine therapy, as well as powerful anticoagulant and thrombolytic agents. However, the prevention of excessive production of pro-inflammatory cytokines in SARS-CoV-2 remains a challenge, and the use of GlucoCorticosteroids (GCs) for this purpose is quite controversial [2]. Scientific sources provide insufficient evidence for the routine use of GCs in the treatment regimens for intensive care units in the severe course of SARS-CoV-2. The advisability of using GCs remains a subject of research and debate [1–3].

The aim of this study was to analyse modern literary sources regarding the latest features of the clinical and pharmacological justification of the use of glucocorticosteroids in SARS-CoV-2 infection in clinical practice.

The nuclear transcription factor (NF-κB) is believed to regulate the production of pro-inflammatory cytokines. It is expressed in activated B-cells (plasma cells) and stimulates the production of pro-inflammatory cytokines TNF-alpha, IL-1-beta, and IL-6, which ensure the spread of inflammation to other cells. Effective suppression of excessive production of pro-inflammatory cytokines is considered a viable approach to preventing fatal lung damage in patients with SARS-CoV-2, and thus, saving lives [2].

GKs are lipophilic molecules that can diffuse through the cell membrane and bind to glucocorticoid receptors, which are located in the cytoplasm of most cells. After modifying the receptors, they diffuse into the nucleus, where they suppress the nuclear transcription factor gene that regulates the genetically determined production of proinflammatory cytokines [4]. Simultaneously, formation of glucocorticosteroid-induced leucine protein occurs, which is an inhibitor of NF-κB [5]. Additionally, GCs cause various biological effects, including the blocking of signals from T-lymphocytes, blocking of neutrophil and mast cell degranulation, macrophage inflammatory activation blockade, and an effect on ion channels of bronchial epithelial cells [6].

On the other hand, GCs are stress hormones synthesized in the adrenal cortex and regulated by the hypothalamic-pituitary-adrenal system. They are synthesized according to circadian cycles under normal conditions. Stress factors and anti-inflammatory cytokines (IL-6, TNF-alpha, IL-1-beta) are able to activate the hypothalamic-pituitary-adrenal system, leading to the synthesis and release of GCs by the adrenal glands, which has an immunomodulatory effect [7]. Corticoid-Binding Globulin (CBG) circulating in the blood binds approximately 90% of cortisol, and determines its inactive form. At the site of inflammation, neutrophil elastase splits CBG, releasing cortisone, where it exerts its anti-inflammatory effect. In addition, the transformation of active cortisol into inactive cortisone is regulated in the tissues by the intracellular enzyme system of 11-beta-hydroxysteroid dehydrogenase type 1 and 2. In this way, inflammatory signals regulate the expression of the above factors, regulating local GCs activity [8].

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Whenever there is an inflammatory process in the body, the hypothalamus-pituitary-adrenal system is stimulated, leading to the activation of the synthesis and release of adrenocorticotropic hormone and cortisol, in direct proportion to the strength of the inflammatory reaction, with subsequent restructuring of the metabolism with the aim of reducing or eliminating the inflammation. At the same time, the anti-inflammatory effect of GCs is realised by inhibiting the nuclear transcription factor that is hyperactivated during SARS-CoV-2 infection [9]. GCs suppress the activation of pro-inflammatory genes that are responsible for the synthesis of pro-inflammatory cytokines, chemokines and prostaglandins, through the induction of 1-kappa-B synthesis, which reduces the translocation of NF-κB into the cell nucleus. The concentration of pro-inflammatory cytokines in blood plasma will determine the severity of the course of SARS-CoV-2 infection. GCs also inhibit the development of fibrosis in tissues recovering after inflammation, which is especially important in SARS-CoV-2 infection, when lung fibrosis often develops in the late stages. In addition, during SARS-CoV-2 infection, a decrease in the activity of angiotensin-2 is noted, while GCs are able to activate it or simulate its expression. Many sources indicate a correlation between the effect of GCs and the severity of the inflammatory process [3; 10]. GCs are able to reduce the concentration of C-reactive protein (CRP) and IL-6 without affecting viral clearance. Therefore, GCs may be prescribed to patients with severe SARS-CoV-2, due to their potent anti-inflammatory and immunomodulatory effects.

The use of GCs is appropriate only in patients with a severe course of SARS-CoV-2 infection, in whom a violation of the functioning of the immune system has been established. Synthetic corticosteroids, such as dexamethasone, prednisolone, and methylprednisolone, have the same biological effects as the endogenous corticosteroids cortisol and hydrocortisone. Moreover, different GCs differ in the strength of interaction with GC receptors, half-life period, duration of action, frequency of administration. In addition, GCs have multiple (pleiotropic) effects, such as the regulation of cell growth, metabolism, reproduction, maturation, inflammation, appetite, and the immune system [11]. High doses of GCs are able to block the interaction of macrophages with proinflammatory cytokines: IL-1-beta, IL-6, IL-12, IL-17, TNF-alpha, granulocyte macrophage colony-stimulating factor, blocking inducible NO-synthase and cyclooxygenase-2 [11]. In endothelial cells, GCs are able to inhibit the expression of adhesion molecules responsible for the recruitment of neutrophils and mononuclear phagocytes from the vascular bed into the tissue during inflammation, thereby suppressing inflammation [12]. The development of resistance of cell receptors to endogenous cortisol during endotoxemia, the action of pro-inflammatory cytokines – TNF-alpha, IL-1, -2, -4, -6, -13, interferon gamma was observed, including under the influence of activation of transcription factors (AR – have a lower ability of cells to respond to endogenous cortisone), and lead to a decrease in the concentration of pro-inflammatory cytokines and a simultaneous increase in the concentration of the anti-inflammatory cytokines IL-4 and IL-10. In addition, synthetic corticosteroids bind to cortisol-binding globulin.

SARS-CoV-2 infection causes damage to the cells of the vascular endothelium, leading to endothelial dysfunction, thrombus formation and microcirculatory dysfunction. And the combination of general systemic inflammation and endothelial dysfunction causes a state of hypercoagulation, with a high risk of developing arterial and venous thrombi. Vascular endothelial cells contain alpha-glucocorticoid receptors in their cytoplasm, which determine the effect of GCs. Therefore, GCs can

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regulate endothelial functions, but their effect, whether normal or proinflammatory, depends on the state of the endothelium. SARS-CoV-2 infection is associated with a reduction or loss of the main functions of the endothelium: vasodilation, fibrinolysis, antithrombotic function. The beneficial effect of GCs is suppression of the endothelial expression of cytokine receptors IL-6, IL-8, G-CSF, VEGF, endothelin-1, NF-κB, arginase-2, cyclooxygenase-2. Therapeutic doses of GCs allow to avoid microcirculation disorders and damage to internal organs. The main effect of GCs in SARS-CoV-2 infection is the simultaneous anti-inflammatory and stabilising effect on the vascular endothelium, reduction of damage to internal organs, tissue swelling and the risk of developing arterial and venous thrombosis [13].

There are data that the use of pulse therapy with GCs means for SARS-CoV-2 infection does not have a significant advantage over the use of high doses of GC (80–240 mg of methylprednisolone). The use of pulse therapy reduces the length of stay of patients in the intensive care unit, but does not have a significant effect on the all-cause mortality due to the frequent development of acute renal failure requiring replacement therapy [14].

An analysis of the literature and recommendations from different countries reveals that specialists have adopted a single-vector approach, which forms the basis of the World Health Organization (WHO) recommendations: 1) the use of GCs is not indicated in patients with a mild course of the disease; 2) systemic GCs therapy is prescribed for patients with a severe or critical course of SARS-CoV-2 infection [15–17].

Thus, the National Health Committee of the People's Republic of China by consensus of experts (2020) recommended the use of GCs in the case of progressive growth of hypoxia, rapidly progressing radiological dynamics in the lungs, hyperactivation of the systemic inflammatory process, recommended methylprednisone in a dosage of 1–2 mg/kg/d IntraVenously (IV) within 3–5 days [18].

The American Thoracic Association, together with the European Respiratory Association (2020), recommended the use of hydrocortisone at a dosage of 200 mg/d IV for 7–10 days in patients on mechanical ventilation and in patients with acute respiratory distress syndrome (ARDS) [19].

The Association of Infectious Diseases of the USA (2020) recommended the appointment of dexamethasone at a dose of 6 mg/day for 10 days or an equivalent dose of another glucocorticoid in critically ill patients with saturation indicators less than 94% who require oxygen support, ventilation or Extracorporeal Membrane Oxygenation (ECMO). Emphasis is placed on the mandatory appointment of GCs in critically ill patients [20]. A similar recommendation was provided by the US National Institutes of Health (2020), which states that GCs are contraindicated in patients who do not need oxygen therapy, but dexamethasone at a dose of 6 mg/d IV or another GCs is indicated in patients on mechanical ventilation – means in an equivalent dose for 10 days [21].

The latest WHO recommendations (2020) emphasise that GCs therapy should only be initiated in patients with a severe course of SARS-CoV-2 infection or who are in critical condition, with dexamethasone at a dose of 6 mg/day or hydrocortisone 50 mg every 8 hours for 7–10 days [22; 23].

A protocol for the management of severe forms of SARS-CoV-2 infection – MATN+ has also been developed and proposed by the US pulmonology centers [24]. It is emphasised that the increasing hypoxemia in patients with SARS-CoV-2 pneumonia is caused by deep dysregulation of the immune system, the development of severe microcirculation disorders, and an increase in the blood coagulation system. The basis of the proposed therapeutic stra-

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tegy for pulmonary involvement in SARS-CoV-2 infection is the combination of GCs (methylprednisolone) with ascorbic acid, thiamine and heparin. Moreover, it is recommended to prescribe intravenous methylprednisolone at a dose of 80 mg/day (40 mg every 12 hours) for 7 days, if necessary, to continue until transfer from the intensive care unit. In patients whose condition is progressively worsening and who have high CRP levels, it is recommended that the dose of methylprednisolone be increased to 80 mg twice daily and, if necessary, to 120 mg twice daily. It is recommended to prescribe ascorbic acid in a dose of 3 g IV 4 times a day for 7 days or before transfer from the intensive care unit under constant glycaemic control. Thiamine is prescribed in a dose of 200 mg IV every 12 hours for 7 days or until transfer from ICU. During the stay in the intensive care unit, the full volume of anticoagulation therapy with enoxaparin at a dose of 1 mg/kg every 12 hours is maintained (the dosage is reduced when the creatinine clearance (ClCr) is less than 30 ml/min). Constant monitoring of anti-Xa factor activity is also carried out. In cases where ClCr <15 ml/min, it is recommended to use unfractionated heparin. High flow oxygen therapy is mandatory, but tracheal incubation should be delayed for as long as possible.

In this protocol, it was additionally recommended to combine the therapy of SARS-CoV-2 infection with the appointment of melatonin at a dosage of 6–12 mg per night, famotidine at a dosage of 40 mg/day, vitamin D at a dosage of 2000–4000 units per day internally, atorvastatin well, in a dosage of 80 mg/day, the purpose of elemental zinc is 50–75 mg/day, magnesium in the form of food additives.

According to the results of the application of the MATN+ protocol, the mortality rate when using methylprednisolone was 6.1%, which is associated with a more adequate dosage of GCs, in contrast to the use of dexamethasone in a dosage of 6 mg, which was proposed after the RECOVERY study (Great Britain). Moreover, both guidelines insisted on the impracticality of using GCs of SARS-CoV-2 infection in the phase of the first clinical manifestations, in patients without respiratory failure, but needed in requiring oxygen support or mechanical ventilation [24].

An analysis of various literature sources has shown that during the treatment of SARS-CoV-2 infection, damage to the hypothalamic-pituitary-adrenal association occurs, and the damage to the adrenal glands is manifested by the development of central hypocorticism, which can persist for up to a year in surviving patients. Perhaps this is a consequence, directly or under the influence of immune mediators, of damage to the pituitary gland or hypothalamus; many histological studies have shown degeneration of neurons and swelling of the hypothalamus [25]. Autopsy studies of patients with a fatal course of SARS-CoV-2 infection showed the presence of degeneration and necrosis in the cortical substance of the adrenal glands, confirming direct damage to adrenal cells by the virus, which, in turn, was confirmed by the presence of viral antigens in the adrenal tissue [26; 27]. In patients with a fatal course of SARS-CoV-2 infection without signs of adrenal insufficiency, microscopic damage to the adrenal glands was found in 46% of cases. Histological findings included non-specific inflammation, fatty dystrophy, vascular thrombosis, necrosis, haemorrhage and local inflammation of the adrenal glands. Thus, among patients with SARS-CoV-2, 23% had adrenal infarction, of which 88% were bilateral, and only 8% had severe adrenal insufficiency [28]. Some researchers noted frequent bilateral hemorrhages in the tissues of the adrenal glands, which were not always accompanied by signs of severe adrenal insufficiency [29–31]. In view of the results obtained, long-term GCs therapy exceeding 2–4 weeks may cause adrenal insufficiency in patients with SARS-

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CoV-2 infection, especially when high therapeutic doses were used, and even without taking into account circadian cycles [32]. Recent studies show that in patients with SARS-CoV-2 there is a relationship between the content of neutrophils and the cortisol levels, so that patients with lymphopenia have higher cortisol levels than patients without lymphopenia. Thus, the presence of lymphopenia can be considered a sign of high endogenous plasma cortisol levels, which also requires a more balanced approach to prescribing GCs therapy [33].

According to the State Register of Medicinal Products of Ukraine, glucocorticosteroids (hydrocortisone, methylprednisolone, dexamethasone), which are registered and indicated for systemic use, including in high therapeutic doses, for the treatment of pathological conditions with a pronounced anti-inflammatory and immunosuppressive effect, have no indications in the instructions for medical the use in SARS-CoV-2 infection, and their use is more considered as symptomatic [34].

Conclusions

The analysis of the scientific literature indicates that today glucocorticosteroid therapy cannot be recommended for routine use in therapeutic practice in patients with SARS-CoV-2 infection. Therefore, in cases of mild SARS-CoV-2 infection where the patient does not require oxygen support, GCs therapy should be contraindicated. Whereas in cases of severe SARS-CoV-2 infection resulting in acute respiratory distress syndrome, oxygen therapy, mechanical ventilation, or ECMO may be required. In such cases, corticosteroids are necessary and may be recommended for mandatory use. There is a need for a generalised definition of the optimal glucocorticosteroid agent, indications, dosage, and duration of use in SARS-CoV-2 infection therapy programs. This should take into account biomarkers of the severity of the inflammatory process and biomarkers of the body's response to glucocorticosteroid agents.

Connection with scientific topics

The study was performed within the framework of the initiative planned research work of the Department of Pharmacology, Clinical Pharmacology and Pharmacy "Pharmacological research of biologically active substances and medicinal products for the development and optimization of indications for their use in medical practice" No.0120U103921, 2020–2024.

Conflict of interest is absent.

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АСПЕКТИ ФАРМАКОТЕРАПІЇ СТЕРОЇДАМИ ПРИ SARS-CoV-2 ІНФЕКЦІЇ (огляд літератури)

За останні роки одним із несподіваних і дуже серйозним викликом для забезпечення здоров'я населення в усьому світі стала пандемія SARS-CoV-2. Причому інфекція SARS-CoV-2 призводила до розвитку гострого респіраторного дистрес-синдрому в результаті надмірного системного запалення, та розвитку поліорганної недостатності, а згодом і смерті. На даний момент, проблема усунення надмірного системного запалення, тобто зниження продукції прозапальних цитокінів при SARS-CoV-2, залишається відкритою. В цьому розрізі застосування ГлюкоКортикоСтероїдів (ГКС) при інфекції спричиненою SARS-CoV-2, залишається досить суперечливим. У протоколах інтенсивної терапії SARS-CoV-2 явно недостатньо підстав для рутинного застосування стероїдів, їх призначення залишається предметом подальших досліджень. У даному огляді наведено аналіз літературних джерел, настанов, сучасних міжнародних рекомендацій з патогенетичної терапії SARS-CoV-2 для запобігання та усунення гіперпродукції прозапальних цитокінів за допомогою застосування ГКС. Метою роботи був аналіз літератури щодо клініко-фармакологічного обґрунтування застосування ГКС при SARS-CoV-2 інфекції в клінічній практиці. Проведений аналіз продемонстрував, що на сьогодні у пацієнтів з SARS-CoV-2 інфекцією терапія ГКС не може бути рекомендована для рутинного застосування в терапевтичній практиці. Так, при нетяжкому перебігу SARS-CoV-2 інфекції, коли пацієнт не потребує кисневої підтримки, ГКС протипоказані. Тоді як при тяжкому перебігу, при гострому респіраторному дистрес-синдромі з тяжкою дихальною недостатністю їх застосування є обов'язковим. Назріла необхідність узагальненого визначення оптимального глюкокортикостероїдного засобу, показань, його дозування та тривалості призначення в програмах терапії SARS-CoV-2 інфекції.

Ключові слова: *системна запальна реакція, прозапальні цитокіни, гіпоталамо-гіпофізарно-наднирникова система, глюкокортикостероїди.*

Надійшла до редакції 15.01.2024

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