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CORONAVIRUS (COVID-19) EPIDEMICS, THE NEWEST AND BIGGEST GLOBAL HEALTH THREATS

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Abstract: Coronaviridae is a peculiar viral family, with a very large RNA genome and characteristic appearance, endowed with remarkable tendency to transfer from animals to humans. Since the beginning of the 21st century, three highly transmissible and pathogenic coronaviruses have crossed the species barrier and caused deadly pneumonia. In this light, the present review provides a systematic update on the current knowledge of the marked global efforts towards the development of antiviral strategies aimed at coping with the infection sustained by SARS-CoV-2 and other human pathogenic coronaviruses, displaying drug resistance profiles[1]. The attention has been focused on antiviral drugs mainly targeting viral protease, RNA polymerase and spike glycoprotein, that have been tested in vitro and/or in clinical trials as well as on promising compounds proven to be active against coronaviruses by an in silico drug repurposing approach.

Keywords:SARS-CoV-2 Coronavirus, antiviral agents, antiviral resistance, RNA polymerase, protease.

Emerging infectious diseases are occurring at an increasing frequency worldwide, having a profound impact on public health. In the past two decades, two highly pathogenic and transmissible coronaviruses emerged causing serious respiratory illness: severe acute respiratory syndrome coronavirus. Coronaviruses are large (with the largest genomes of all RNA viruses), enveloped, with a very characteristic appearance, positive-sense single-stranded RNA viruses classified into 4 genera: α-, β-, δ- and γ-coronaviruses. Members of the subfamily Coronavirinae are widespread among mammals, often causing only mild respiratory or enteric infections. Over 60 coronaviruses have been isolated from bats (BatCoV) and most of these are in the genus β-coronavirus. The β-coronavirus genus comprises the human SARS-CoV-1 and -2 (belonging to the subgroup 2b), MERS-CoV (subgroup 2c), and HCoV-OC43 and HCoV-HKU1 (subgroup 2a). [2]

This review provides a comprehensive overview of the current and innovative antiviral strategies targeting viral protease, RdRp and spike glycoprotein, that have been proposed to cope with the infection sustained by SARS-CoV-2 and other pathogenic human coronaviruses. Thanks to the analysis of a large sequence datasets, a detailed information of the conserved regions in 3CL-PR, RdRp and spike across human coronaviruses is also presented. These regions can represent novel druggable targets for compounds with pan anti-coronavirus activity. Several clinical trials are ongoing to test whether protease inhibitors such as lopinavir, ritonavir and darunavir used for HIV treatment, or danoprevir used for HCV treatment, are also effective against SARS-CoV-2 .

Concerning nucleoside analogues, those in the form of adenine or guanine analogues, target the RdRp and block viral RNA synthesis in a broad spectrum of RNA viruses, including human coronaviruses[3]. The coronavirus spike protein is a multifunctional molecular machine that mediates coronavirus entry into host cells. It first binds to a receptor on the host cell surface through its S1 subunit and then fuses viral and host membranes through its S2 subunit. Two domains in S1 from different coronaviruses recognize a variety of host receptors, leading to viral attachment. The spike

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protein exists in two structurally distinct conformations, prefusion and postfusion [4]. The transition from prefusion to postfusion conformation of the spike protein must be triggered, leading to membrane fusion. This article reviews current knowledge about the structures and functions of coronavirus spike proteins, illustrating how the two S1 domains recognize different receptors and how the spike proteins are regulated to undergo conformational transitions. I further discuss the evolution of these two critical functions of coronavirus spike proteins, receptor recognition and membrane fusion, in the context of the corresponding functions from other viruses and host cells [5]. The main target cells for coronaviruses are cells of the alveolar epithelium, in the cytoplasm of which the virus is replicated. After the virions are assembled, they pass into cytoplasmic vacuoles, which migrate to the cell membrane and exit into the extracellular space by exocytosis. The expression of virus antigens on the cell surface does not occur before the virions exit the cell, therefore, antibody formation and interferon synthesis are stimulated relatively late. Education syncytia under the influence of the virus makes it possible for the latter to spread rapidly into the tissue. The effect of the virus causes an increase in the permeability of cell membranes and increased transport of albumin-rich fluid into the interstitial lung tissue and the lumen of the alveoli. At the same time, the surfactant is destroyed, which leads to the collapse of the alveoli, as a result of a sharp violation of gas exchange, acute respiratory distress syndrome (ARDS) develops. The immunosuppressive state of the patient contributes to the development of opportunistic bacterial and mycotic infections of the respiratory tract[6].

To date, there is no evidence of the effectiveness of any drugs in COVID-19 As part of the provision of medical care, monitoring of the patient's condition is necessary to identify signs of clinical deterioration, such asrapidly progressive hypertension and sepsis, the appointment of therapy in accordance with the patient's condition. Patients infected with SARS-CoV-2 should receive supportive symptomatic therapy. An analysis of the literature data on the clinical experience of managing patients with SARS-CoV and MERS-CoV coronaviruses, allows us to identify several etiological drugs that are usually used in combination. These include ribavirin, lopinavir+ritonavir [6] and interferon preparations. However, the results of the use of these drugs do not allow us to draw an unambiguous conclusion about their effectiveness / inefficiency, and therefore their use is permissible by decision of the medical commission in accordance with the established procedure if the possible benefit to the patient exceeds the risk. The use of etiotropic drugs is justified in the case of moderate to severe infection, when the intended benefit exceeds the potential risk of adverse events. The list of possible medications for the etiotropic therapy of infection, caused by the SARS-CoV-2 coronavirus is indicated in Temporary methodological recommendations of the Ministry of Health of the Russian Federation (Version 4). According to WHO recommendations, it is possible to prescribe drugs with the expected etiotropic efficacy of off-label, while their use must comply with ethical standards recommended by WHO and be carried out on the basis of Federal Law No. 323-FZ of November 21, 2011 "On the Basics of Public Health Protection in the Russian Federation", Federal Law of April 12, 2010. No. 61-FZ "On the Circulation of Medicines", the National Standard of the Russian Federation GOST R ISO 14155-2014 "Good clinical Practice", Order of the Ministry of Health of the Russian Federation dated April 1, 2016 No. 200n "On Approval of the Rules of good clinical practice" (registered by the Ministry of Justice of the Russian Federation on August 23 2016, registration No. 43357), the Helsinki Declaration of the World Medical Association (WMA) on the Ethical Principles of Conducting Research with Human Participation as a Subject, declared at the 64th General Assembly VMA, Fortaleza, Brazil, 2013 In February of this year, in a joint project, Chinese and German scientists synthesized a special group of drugs (alpha-ketoamides) that have the

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ability to inhibit the main proteases of various viruses, including SARS-CoV-2.The researchers determined the three-dimensional crystal structure of the main protease SARSCoV-2 and modified the alpha-ketoamide molecule due to the P3-P2 amide bond included in the pyridone ring, which contributed to the specific inhibition of coronaviruses. Due to this , the half-life of alpha-ketoamide has increased three times, and the solubility was 19 times, which, however, led to a slight decrease in efficiency. In an experiment on mice with inhalation, alpha-ketoamide demonstrated pronounced pulmonary tropism and no side effects [7]. Pathogenetic therapy includes the introduction of a sufficient amount of liquid into the body (up to 3.5 liters per day) in the absence of contraindications, enterosorbents (colloidal silicon dioxide, polymethylsiloxane polyhydrate and others). In patients in serious condition, infusion therapy is carried out under the control of arterial pressure blood pressure, auscultative picture of the lungs, dieresis and other indicators. In order to prevent cerebral edema and pulmonary edema, it is advisable for patients to undergo infusion therapy against the background of forced diuresis. In order to improve the discharge of sputum with a productive cough, acetylcysteine, ambroxol, carbocysteine and other combined drugs are prescribed. In the presence of bronchoobstructive syndrome, inhalation bronchodilator is actively used (through a nebulizer) therapy using salbutamol, phenoterol and combined agents.[8]

Environmental change, climate warming, an increase in population density, the development of biotechnology and other factors provoke the emergence, and increasing migration flows and the processes of economic globalization contribute to the spread of new infections. The biological threats associated with epidemics of infectious diseases are global in nature. The COVID-19 epidemic is not the last threat in the 21st century. All countries should be ready for coordinated prevention actions in Environmental change, climate warming, an increase in population density, the development of biotechnology and other factors provoke the emergence, and increasing migration flows and the processes of economic globalization contribute to the spread of new infections. The biological threats associated with epidemics of infectious diseases are global in nature. The COVID-19 epidemic is not the last threat in the 21st century. All countries should be ready for coordinated prevention actions and the spread of infections, their timely diagnosis, the development of treatment and prevention methods, and the creation of vaccines.

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