BRIEF COMMUNICATION

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CURRENT COVID-19 PANDEMIC AND PHARMACOLOGICAL AGENTS

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Information about drugs capable of reducing virus replication and cytokine storm in COVID-19 patients is presented.

Keywords: COVID-19; IL-6; chloroquine; hydroxychloroquine; tocilizumab.

The onset of COVID-19 pandemic required attracting large resources and qualified medical staff in effort to reduce mortality and disability of patients. Among numerous measures proposed by the Russian Ministry of Health for fighting this infection, significant role belongs to well-known pharmaceuticals [1], the application of which must reduce pandemic consequences. Unfortunately, there are no special antiviral drugs capable of reducing causative agent permeation into cell populations of breathing passages and arresting virus replication and/or preventing its penetration (after the mature virus form development) into intact cells. This circumstance, together with concomitant diseases frequently present in COVID-19 patients hinders providing them with effective drugs. High level of heavy COVID-19 form development (up to 25%) has inspired the search for pharmacological agents among existing drugs administered in the treatment of various disorders, which might be also effective against COVID-19.

The official list of drugs [1] includes chloroquine, hydroxychloroquine and mefloquine (quinoline derivatives) belonging to the group of antimalarial drugs possessing hematoschizotropic properties, which are administered for the prophylaxis and treatment of malaria [2]. At first glance, inclusion of these drugs in the list of agents recommended for the treatment of COVID-19 can seem bewildering. However, these drugs are weak bases that are capable of accumulating in organelles, including lysosomes (featuring acid pH) of cells (pneumocytes) in lower respiratory tracts, which interact with viral particles, violate their replication, and can also influence their binding with surface cell receptors [7, 8]. It should also be noted that the antiviral effect of these compounds *in vitro* is achieved at concentrations comparable to those formed during clinical application. This behavior has been observed in investigations of the action of these drugs on HIV, Ebola virus, Dengue virus, etc. [4, 7].

Patients suffering of COVID-19 in a heavy form have been noted to possess increased level of C-reactive protein, TNF-α, IL-6, IL-8, and some other biologically active substances. In addition, they also exhibit signs of hypercoaguation, increased intravascular coagulation, and vessel damage [7]. The activation of various cytokines is accompanied by so-called "cytokine storm" syndrome (CSS), manifestations of which lead eventually to the development of acute respiratory distress syndrome (ARDS) [6]. Autopsy reveals pronounced proliferation of alveolar cells, infiltration of monocytes, lymphocytes, and plasma cells, lung tissue interstitial disorder, and accumulation of some immune cells [5]. This situation requires treating COVID-19 patients with immunodepressants, some of which (including quinoline derivatives) are more preferred. In view of the immunomodulator activity, these drugs are also widely used in rheumatology for the treatment of lupus erythematosus and rheumatoid arthritis. It was reported that CSS could weaken under the action of quinolone derivatives. In the therapy of COVID-19 patients, quinoline derivatives are frequently combined with azithromycin and clarithromycin (macrolide antibiotics) known to exhibit high anti-inflammatory activity [6]. At the same time, the main counter-indication to the administration of chloroquine and other drugs of this group is bacterial sepsis [1].

A key role in the development of CSS belongs to interleukin IL-6 which is released from pathogenic T-lymphocytes and "inflammatory" monocytes and binds to the corresponding receptors. Manifold growth of IL-6 secretion gives rise to cascade processes leading to edema formation and inflammatory infiltration of lung tissue, resulting in sharp degradation of lung function. In this context, the possibility of supporting COVID-19 treatment by drugs negatively influencing IL-6 mediated reactions can play a positive role. Tocilizumab, which has been recently adopted for practical application to COVID-19 treatment, is based on anti-IL-6 antibodies and has been successfully used for the therapy of patients with rheumatoid arthritis [3, 5]. However, in patients suffering of COVID-19 in a heavy form, this drug attenuates immune response to the action of viral particles, while not influencing the replication process [3]. The administration of tocilizumab may be accompanied by the activation of opportunistic infections

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(tuberculosis mycobacterium, pathogenic and conditionally pathogenic fungi, etc.).

The possibility of prescribing glucocorticosteroids (GCSs) possessing the properties of antidepressants and anti-inflammatory agents [2] to COVID-19 patients is still under discussion. Many experts negatively meet the idea of using these drugs because of their influence on the clearance of viral particles, the more so that GCSs have numerous side effects of their own [7].

At present, it is commonly accepted that receptors targeted by COVID-19 causative agent represent angiotensin converting enzyme 2 (ACE2), a protein localized on the cell surface. This receptor is present in heart, vessels, kidney, and alveolar epithelial cells. Virus permeates into cell populations by means of endocytosis – a process controlled to a considerable extent by adaptor-associated protein kinase 1 (AAK1). Blocking of this enzyme can violate virus penetration into the cell. Possible inhibitors of this process include baricitinib – a drug belonging to the group of agents blocking the activity of Janus kinase (JAK). In addition, this drug inhibits the activity of many cytokines involved in the process of inflammation – in particular, interferon б playing important role in reducing viral activity [8]. Clinical trials of the efficiency of baricitinib and some other JAK inhibitors on patients suffering of COVID-19 are planned to be held in 2020.

Therefore, published data summarized above show evidence of rather insignificant possibilities of the pharmacological treatment of COVID-19 using existing drugs and, hence, point to the need in active search for new effective antiviral agents.

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