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Covid-19 Infection: Prerequisites for New Areas of Research

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Abstract- The pandemic of COVID-19 infection caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) has posed a significant threat to global health. Now, we have witnessed an unsurpassed increase in the number of clinical trials worldwide. In clinical trials old and new drugs are tested as potential treatments either for their direct anti-viral activity, or for their ability to provide management of respiratory and cardiovascular symptoms and complications, characteristic of COVID-19. Despite the worsening trends of COVID-19, no drugs are validated to have significant efficacy in clinical treatment of COVID-19 patients in large-scale studies. Such a strategy is likely to give rise to a range of safety and efficacy challenges that could be addressed through preliminary pharmaco-genetic research on identification of risk groups for personification of therapy approach. Addressing the personification of drug treatment COVID-19 becomes an urgent need to interpret the conflicting results of clinical trials and establish the apparent efficacy of any particular drug.

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Covid-19 Infection: Prerequisites for New Areas of Research

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Abstract- **The pandemic of COVID-19 infection caused by severe acute respiratory syndrome coronavirus (SARS-CoV-2) has posed a significant threat to global health. Now, we have witnessed an unsurpassed increase in the number of clinical trials worldwide. In clinical trials old and new drugs are tested as potential treatments either for their direct anti-viral activity, or for their ability to provide management of respiratory and cardiovascular symptoms and complications, characteristic of COVID-19. Despite the worsening trends of COVID-19, no drugs are validated to have significant efficacy in clinical treatment of COVID-19 patients in large-scale studies. Such a strategy is likely to give rise to a range of safety and efficacy challenges that could be addressed through preliminary pharmaco-genetic research on identification of risk groups for personification of therapy approach. Addressing the personification of drug treatment COVID-19 becomes an urgent need to interpret the conflicting results of clinical trials and establish the apparent efficacy of any particular drug.**

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I. Introduction

The recent outbreak of COVID-19 in Wuhan has become a worldwide health emergency. An analysis of the global situation with COVID-19 today convincingly indicates that humanity has faced a serious threat associated with the high prevalence of coronavirus infection [1]. The global importance of the COVID-19 pandemic problem for the world community also proves the exponential increase in the number of publications devoted to this problem. Since the beginning of 2020, the number of publications on the problem of COVID-19 has grown from several tens to several thousand and today it continues to increase [2]. Nevertheless, despite the sharp increase in relevant information and the replenishment of our knowledge with new data about this infection, so far there are much more questions than answers. A comprehensive analysis of the recent contradictory, and sometimes even opposing opinions of scientists on this issue makes a deep understanding of not only the epidemiological process of coronavirus infection, but also the pathophysiological processes associated with the expansion of the virus into the body and, above all, with the response of the organism in the form of an immuno-inflammatory response to viral aggression [3]. And this should be the basis of ongoing developments in the field of drug treatment of COVID-19 infection.

Currently known mechanisms for the development of pathological processes in coronavirus infection include: 1) multi-tissue expression of ACE2 receptors [4]; 2) a pronounced systemic increase in inflammatory cytokines and mediators; 3) diffuse endotheliitis and 4) impaired iron metabolism homeostasis, leading to oxidative stress and inflammatory response.

The SARS-CoV-2 virus was found to enter the host cells through the ACE2 receptor on the surface of cell membranes, where it encounters an innate immune response that inhibits viral replication through expression of interferon (IFN) -stimulated genes (ISGs) and the release of pro-inflammatory cytokines such as IL1b, IL-2, IL-7, TNF-a, GSCF, MCP1, etc. [5]. How coronavirus manages to evade the inhibitory function of ISG has not yet been fully resolved (it is only known that this virus has 8 proteins that can block interferon), but in the future the clinic of seriously ill with COVID-19 indicates an excessive immune response with such a huge amount of cytokines in the tissues that such a condition was described as a "cytokine storm". Moreover, an increase in the concentration of anti-inflammatory cytokines such as IL10 and IL4was completely unexpected, which is considered unusual for the acute phase of a viral infection.

Since ACE2 is detected in the greatest amount on the surface of the cell membranes of the pulmonary alveoli and blood vessels, apparently, therefore, the main place of aggressive exposure to the SARS-CoV-2 virus is the lungs. However, since this protein is also spread in other organs and systems, in particular, in the blood vessels of the kidneys, intestines, liver, heart, the developing pathological process leads in severe cases

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to rather rapid development of disorders in many organs, which turns into multiple organ failure.

In addition, it was shown that the protein sequences of the SARS-CoV-2 virus can form a complex with porphyrin and also affect heme in the 1-β chain of hemoglobin, leading to iron dissociation [6]. In turn, an increase in iron levels can contribute to the development of viral infections [7] associated with a number of respiratory diseases, including acute respiratory distress syndrome and pulmonary fibrosis.

Therefore, the COVID-19 virus for the most part only triggers the pathological process, and the further development of events will depend on the nature of the reaction of the body's defense systems, i.e. the body in response to viral aggression will fiercely fight against its own substrates of the body's compensatory systems, similar to the "cytokine storm" and the development of oxidative and other stress syndromes, much like sepsis or autoimmune diseases.

Apparently, the more severe course of this infection in people with concomitant chronic diseases, especially autoimmune genesis or using ACE2 in their pathogenesis, also indicates that the initially impaired immune balance in the body serves as an engine for the development of an inferior and perverse response in case of viral aggression and will determine the nature and severity of the course of the pathology [8]. In addition, recently revealed positive results from the use of basic anti-inflammatory drugs and the modified biological gene used to treat rheumatoid arthritis can also confirm this assumption.

Therefore, current evidence suggests that the pathogenesis of COVID-19-induced pneumonia closely resembles autoimmune / autoinflammatory syndromes, thereby supporting attempts to use antirheumatic drugs of a chemical or biological nature. However, a number of questions appear here. For example, as indicated by Caso et al.[9],emphasizing the similarities between COVID-19 and autoimmune / autoinflammatory syndromes, it remains to be determined whether a genetic predisposition can contribute to the variability of clinical phenotypes. Another important issue is the identification of triggers responsible for the development of lung damage and hyperinflammation in the late phases of COVID-19. Of course, a large amount of evidence indicates ACE2, used by SARS-CoV-2 for entry into the cell, however, whether there is direct relationship between the viral damage of ACE2 and the development of hyperinflammation with lung disorders is still not very clear. And the answer obtained can be quite significant, because if it is mediated, the number of viral load will play a smaller role compared with the body's genetic predisposition to a hyperinflammatory response. Based on the preliminary results available today that it is not possible to confirm the relationship between the progression of lung damage and activation of viral replication [10], apparently the last assumption will gather all the chances to reflect the real situation.

Since the reactions of the body's protective and adaptive systems to any aggression have individual characteristics and are genetically determined, belonging to a particular variant of the polymorphism of genes that control these body functions can be of limited value in predicting the likely response of the body to infection [11]. These markers include gene polymorphisms of the angiotensin-converting enzyme, tumor necrosis factor, interleukins, HLA systems and others. Such an approach to solving the problem would make it possible to determine in advance a predisposition to the severe course of coronavirus infection, form risk groups and their stratification, and also develop a new, scientifically based strategy and tactics for administering patients with this infection. Moreover, this would be a good help for the development in our country of such a direction as the development of gene modified biological preparations based on genomic, epigenomic and transcriptome approaches. Such circumstances open up new horizons for the prevention and control of coronavirus infection in general.

There is currently no specific effective antiviral treatment for COVID-19. Based on in-vitro data and available information on safety and biological efficacy, the World Health Organization (WHO) prioritized several drugs for further research at COVID-19 and recommended them for evaluation in the context of the "Solidarity" clinical trials (www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en). For this study, WHO selected an experimental antiviral agent, remdesivir; used for the treatment of malaria-chloroquine (or its chemical counterpart, hydroxychloroquine); a combination of HIV drugs-lopinavir-ritonavir; and the same combination plus beta interferon - the messenger of the immune system.

Although clinical trials are still ongoing, negative actions are already being identified. So, in relation to chloroquine, its well-known toxic and side effects began to appear, and its cardiotoxic effect in the form of a change in heart rhythm has already led to deaths in Brazil, due to which a number of tests were stopped (https://www.nytimes.com/2020/04/12/health/chloroquine-coronavirus-trump.html).

The very first test of a combination of lopinavir-ritonavir drugs in Wuhan (China) for 199 patients with COVID-19 did not lead to statistically significant differences between the groups with and without these drugs, which was explained by the possible too late treatment of severe patients [12]. Recently, developed by Gilead Sciences specifically to combat the Ebola virus, the drug remdesivir showed excellent performance in vitro against the SARS and MERS viruses. However, in practical terms, this drug was not able to effectively help patients with Ebola virus during the 2019 outbreak in the

Democratic Republic of the Congo, but some of its negative manifestations (for example, nausea, vomiting, rectal hemorrhage and liver toxicity) were already known.

Of course, research is ongoing and final conclusions will be drawn later. Now the WHO International Clinical Trials Registration Platform has already registered over 700 clinical trials of various drugs and treatments of COVID-19 (https://apps.who.int/trialsearch).

As a result of the accumulation of knowledge on the pathophysiology of COVID-19, in addition to the use of certain antiviral drugs, many medicinal substances that are commonly used to treat other autoimmune and metabolic diseases have been proposed as possible treatment methods [13].

Currently, the number of ways to combat SARS-CoV-2 that are undergoing clinical trials has reached 62. Moreover, fifteen procedures are based on the use of both known and new antiviral drugs: lopinavir and ritonavir[14], arbidol, hydroxychloroquine, chloroquine, DAS181, remdesivir, azvudine, baloxavir, azithromycin, amiodarone, verapamil, ivermectin, APN01, alvesco, CYNK001, virazole, as well as convalescence plasma therapy and Yeliva. Whereas, the second line of treatment is based on the use of anti-inflammatory drugs and immunomodulators, including glucocorticoids, tocilizumab, jacotinib hydrochloride, leukin, lenzylumab, CD24Fc, colchicine, tradipitant, siltuximab, anakinra, sarilumab, vazepal 1, IFX-1,leronlimab, aviptadil, fingolimod, piklidenozon, selinexor, akalabrutinib, clazacizumab, zanubrutinib, gimsilumab, TJ003234, halidesivir, etc.

In addition, a test was undertaken of the following drugs used to treat pneumonia after a viral infection: danoprevir + ritonavir, darunavir, ruxolitinib, bevacizumab, AiRuiKa ™, tofacitinib, deferoxamine and meplazumab; as well as some drugs used to prevent organ failure, such as: valsartan, dapagliflozin, losartan [15].

If we consider drugs that are only offered for clinical trials, their number already exceeds one hundred, they affect many other, including recently identified, pathogenetic links, they have a diverse mechanism of action, they are well known and are already effectively used to treat many, including non-infectious diseases (premarin, pioglitazone, melatonin, thalidomide, pirfenidone, chlorpromazine, sildenafil, cyclosporine, ouabain, bufalin, dapagliflosin, dapsone, doxycycline, amantadine, vitamin D, etc.) [16].

On this background, as one of the important aspects of the problem of COVID 19 infection, in terms of interpreting the conflicting results of clinical trials and quickly establishing the apparent effectiveness of a particular drug, the issue of personifying its medical treatment becomes a question. This problem is associated with the individual characteristics of the patient's body in the manifestation of the reaction to the drug, because now there are enough examples when similar drugs in similar doses seemed to give different results in almost identical clinical situations both in terms of effectiveness and safety.

This is indeed a difficult question, because it is associated with the functioning of a number of body systems that are involved in the processes of absorption, adsorption, bioavailability, distribution, transportation, metabolism and elimination of drugs. Moreover, the initial state of these systems and their full functioning regulates the formation of an adequate pharmacological response to a specific drug.

Perhaps this is the basis of the preliminary conflicting results of research conducted under the "Solidarity" program. After all, it is known that remdesivir is a prodrug [17], which means that its action will be fully manifested only after its metabolism inside the cell, and the extent of readiness of the enzymes metabolizing it before taking the drug is not established. The lopinavir / ritonavir complex is a protease inhibitor used in the combination therapy of immunodeficiency in a person infected with HIV. Since lopinavir inhibits the cleavage of the gag-pol protein, while ritonavir inhibits the cleavage of the precursor of this protein and at the same time the metabolism of lopinavir through the P-450 cytochrome system (CYP3A4), to increase the concentration of lopinavir, these drugs are always prescribed together as a complex. However, depending on the initial state of the metabolizing enzymes, both toxic properties and insufficient effectiveness of these drugs may occur. The same can be noted for chloroquine, which has been used worldwide for more than 70 years as an antimalarial drug.

It is known that the above systems that regulate the fate of drugs in the body, like other components, are genetically controlled. Enzymes carrying out transmembrane transport of drugs, their efflux from the cell, as well as biotransformation and elimination from the body are carried out by expression of the corresponding genes, in particular glycoproteins of the MDR1 type, a family of cytochrome isoforms. The candidate genes responsible for the pharmacokinetics of drugs have numerous mutant variants that contribute to the formation of an appropriate response of the body to drugs.

Based on the experience of prescribing antiretroviral drugs for the treatment of HIV infection, some of which are effective against COVID-19, the question of preliminary pharmacogenetic studies has long been raised. So, the effectiveness of a number of drugs widely used in HIV infection is very dependent on the single nucleotide polymorphism of the HLA system genes, cytochrome P-450 and glycoprotein carriers, for example: for abacavir - HLA B * 5701, HLA-DR7 and HLA-DQ3 genotypes [18], for nevirapine - HLA-DRB1 * 01: 01, HLA-cw8 / HLA-B14, ABCB1 (MDR1) 3435C> T,

cytochrome P-450: CYP3A4 \ 5, CYP2D6 and CYP2B6; for the efavirenz, CYP2B6 516G> T, 983T> C, 785A> G and 21563C> T, CYP2A6 -48T> G. A similar CYP3A5 gene polymorphism is closely associated with faster clearance of indinavir, an antiretroviral drug from the class of protease inhibitors that is currently undergoing clinical trials against COVID-19, like other drugs of this class: lopinavir, ritonavir and darunavir.

Extensive information on the pharmacogenetics of almost all currently used drugs, the activity of pharmaco-metabolizing enzymes and individual body parameters that determine the effectiveness of the used drugs is well reflected in many publications [19]. Therefore, we believe that the study of the variants of carriage of the polymorphic diversity of these genes from the standpoint of the efficacy and safety of the pharmacotherapy of COVID-19 infection would significantly increase the effectiveness of therapeutic measures for this pathology. And the accumulation of data on preliminary pharmacogenotyping of people from the perspective of the possible choice of certain drug groups for the treatment of this pathology would contribute to personification and significantly reduce the risk of side effects.

The above mentioned points, in our opinion, is a definite prerequisite for planning a vector of scientific research in the future. Of course, it is premature to talk about conducting such scientific research now, at the height of the epidemic, but we believe that there is a need to conduct such research in the future, the results of which will serve as a theoretical foundation for the development of effective platforms for the prevention and control of not only coronavirus, but also with any other infections.

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