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GENETIC PREDICTORS OF SEVERITY AND EFFICACY OF COVID-19 PHARMACOTHERAPY

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The pandemic of the novel coronavirus infection 2019 (COVID-19) has changed many aspects of our lives and initiated numerous studies aimed at finding the factors that determine different courses of this infectious disease. The studies aimed at finding predictors of the severe course of this novel coronavirus infection, as well as the factors that determine the efficacy and safety of this disease pharmacotherapy, are acquiring special social significance.

The aim of this work is to find and summarize information on genetic predictors of severe COVID-19, as well as pharmacogenetic aspects that determine the variability of the therapeutic response to the drugs recommended for COVID-19 treatment.

Materials and methods. The article provides a review of scientific results on the research of gene polymorphism that determine a body's response to the introduction of SARS-CoV-2 infection and the effects of pharmacotherapy for this disease, obtained from open and available sources within the period of 2019 – March 2021. The search was conducted in the following electronic databases: PubMed, Cochrane Library, ClinicalTrials.gov; Elibrary, Scopus. The main search inquiries were: "predictors + severe course + COVID-19", "genetic variations + COVID-19", "pharmacogenetics + COVID-19", "gene polymorphism + SARS-CoV-2", "pharmacotherapy + gene polymorphism + COVID-19" in both Russian and English.

Results and conclusion. The exploratory research detailing the mechanisms of infecting with SARS-CoV-2, the variability of the disease severity and the individual characteristics of therapeutic responses to the drugs used, are being actively carried out by scientists all over the world. However, most of their scientific projects are diverse, and the possible predictors of a severe course of COVID-19 found in them, have not been confirmed or investigated in subsequent studies. A generalization of the individual studies results of the genetic predictors concerning COVID-19 severity and effectiveness of its pharmacotherapy, can become the basis for further search and increase the reliability of the data obtained in order to develop a strategy for preventing the spread of COVID-19 infection, to identify potential targets of the treatment, and develop the protocols for optimizing this disease pharmacotherapy.

Keywords: COVID-19; pharmacotherapy; gene polymorphism; pharmacogenetics; SARS-CoV-2; predictors

Abbreviations: COVID-19 – coronavirus disease-2019; SARS-CoV-2 – severe acute respiratory syndrome–associated coronavirus disease, COVID-19 etiology; WHO – World Health Organization; GWAS – Genome-Wide Association Studies / полногеномный поиск ассоциаций; ACE – angiotension-converting enzyme; AGTR1/2 Angiotensin II receptor Type 1 and Type 2; OR – odd ratio; TMPRSS2 – Transmembrane protease, serine 2; T NF-κB – Transcriptional nuclear factor-kB; DPP4 – Dipeptidyl-peptidase 4; MERS-CoV – coronavirus, Middle East respiratory syndrome etiology; TLR – Toll-like receptor; RNA – ribonucleic acid; IRF – Interferon Regulatory Factor; INF – interferon; IL – Interleukin; HLA – Human Leukocyte Antigens; HIV – human immunodeficiency virus; TNF – Tumor necrosis factor; TGF – Transforming growth factor; CYP – Cytochrome P450; GCSs – glucocorticosteroids; ARDS – acute respiratory distress syndrome; ATP – adenosine triphosphate; CI – confidence interval; RR – relative risk; Ig – immunoglobulin

ГЕНЕТИЧЕСКИЕ ПРЕДИКТОРЫ ТЯЖЕСТИ ТЕЧЕНИЯ И ЭФФЕКТИВНОСТИ ФАРМАКОТЕРАПИИ COVID-19

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Пандемия новой коронавирусной инфекции COVID-19 изменила многие аспекты нашей жизни и инициировала многочисленные исследования, направленные на поиск факторов, определяющих различное течение этого инфекционного заболевания. Особую социальную значимость приобретают исследования, направленные на поиск предикторов тяжелого течения новой коронавирусной инфекции, а также факторов, определяющих эффективность и безопасность фармакотерапии этого заболевания.

Цель. Целью настоящей работы является поиск и обобщение информации о генетических предикторах тяжелого течения COVID-19, а также фармакогенетических аспектах, определяющих вариабельность терапевтического ответа на рекомендованные лекарственные препараты для лечения COVID-19.

Материалы и методы. В статье представлен обзор результатов научных исследований по изучению полиморфизма генов, определяющих ответ организма на внедрение SARS-CoV-2 инфекции и эффектов фармакотерапии данного заболевания, полученных из открытых и доступных источников за период 2019- март 2021 гг. Поиск проводился в электронных базах данных: PubMed, Cochrane Library, ClinicalTrials.gov; Elibrary, Scopus. Основные поисковые запросы: «предикторы + тяжелое течение + COVID-19», «генетические вариации+COVID-19», «фармакогенетика+COVID-19», «полиморфизм генов + SARS-CoV-2», «фармакотерапия+полиморфизм генов + COVID-19». Поисковые запросы выполнялись на русском и английском языках.

Результаты и заключение. Поисковые научные исследования, детализирующие механизмы заражения SARS-CoV-2, вариабельность тяжести течения заболевания и индивидуальные особенности терапевтического ответа на применяемые препараты, активно проводятся учеными разных стран мира. Однако большинство их научных проектов являются разнонаправленными, а найденные в них возможные предикторы тяжелого течения COVID-19 не подтверждены или не изучены в последующих исследованиях. Генетически обусловленная гетерогенность иммунного ответа организма на SARS-CoV-2 инфекцию требует дальнейшего изучения, что во многом связано с отсутствием однозначного мнения о ведущем механизме, определяющем тяжесть этого заболевания. Обобщение результатов отдельных исследований генетических предикторов тяжести течения и эффективности фармакотерапии COVID-19 может стать основой для дальнейшего поиска и повышения достоверности полученных данных с целью разработки стратегии предупреждения распространения инфекции COVID-19, определения потенциальных мишеней таргетной терапии, а также разработки протоколов оптимизации фармакотерапии этого заболевания.

Ключевые слова: COVID-19; фармакотерапия; полиморфизм генов; фармакогенетика; SARS-CoV-2; предикторы

Список сокращений: COVID-19 – коронавирусная инфекция 2019 года; SARS-CoV-2 – коронавирус, этиология COVID-19; ВОЗ – Всемирная организация здравоохранения; GWAS – Genome-Wide Association Studies / полногеномный поиск ассоциаций; АПФ – ангиотензин-превращающий фермент; AGTR1/2 Angiotensin II receptor type 1 and type 2 / Рецептор ангиотензина II типа 1 и 2; ОШ – отношение шансов; TMPRSS2 – Transmembrane Serine Protease 2 / трансмембранная сериновая протеаза типа 2; NF-κB – Nuclear factor-κB / транскрипционный ядерный фактор κB; DPP4 – Dipeptidyl-peptidase 4 / дипептидилпептидаза 4; MERS-CoV – короновирус, этиология ближневосточного респираторного синдрома; TLR – Toll-подобные рецепторы; РНК – рибонуклеиновая кислота; IRF – Interferon Regulatory Factor / регуляторный фактор интерферона; ИНФ – интерферон; IL – Interleukin / интерлейкин; HLA – Human Leukocyte Antigens / главный комплекс гистосовместимости; ВИЧ – вирус иммунодефицита человека; TNF – Tumor necrosis factor / фактор некроза опухоли; TGF – Transforming growth factor / трансформирующий фактор роста; CYP – cytochrome P450 / ферменты цитохрома; ГКС – глюкокортикостероиды; ОРДС – острый респираторный дистресс-синдром; АТФ – аденозинтрифосфат; ДИ – доверительный интервал; OR – относительный риск; Ig – иммуноглобулины

INTRODUCTION

The pandemic of the novel coronavirus infection COVID-19 has changed many aspects of our lives and initiated numerous studies aimed at finding the factors that determine different courses of this infectious disease. It is known that more than 40% of people convey SARS-CoV-2 asymptomatically; in addition, a part of the population has a natural resistance to it and does not manifest the disease even with a high viral load [1]. The other pole of the individual reactivity is patients with a severe course of infection who are hospitalized in the intensive care unit with symptoms of acute respiratory distress syndrome and a multiple organ failure. In this group, the mortality rate is over 40% [2]. According to WHO dated March 31, 2021, 2,769,696 confirmed deaths from COVID-19 for 126,372,442 cases were registered in the world[1]. A lot of modern studies are aimed at finding predictors of the severe course of this novel coronavirus infection. Some of them are devoted to clinical factors: for example, a male gender, an old age and comorbid backgrounds are more often associated with a severer course of the disease [3, 4]. Other studies are looking for individual genetic variations that determine differences in the immune response to the SARS-CoV-2 infection and can explain the clinical course of COVID-19, as well as differences in morbidity and mortality from the SARS-CoV-2 infection in different countries [5, 6].

The correlation between the COVID-19 severity and certain allelic genes variants responsible for the immune response, is very important since it can be used to identify a population with a predisposition to a severer course of infection and to determine a vaccine prevention strategy. This data can be used to develop targeted therapeutic approaches, as well as to select specialists to work with COVID-19 patients in case of a high probability of mild and asymptomatic courses.

[1] WHO report on the current situation with COVID-19 in the world (as of 31 March 2021) Available from: https:// www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---31-march-2021

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THE AIM of this work is to find and summarize information on genetic predictors of severe COVID-19, as well as pharmacogenetic aspects that determine the variability of the therapeutic response to the drugs recommended for COVID-19 treatment.

MATERIALS AND METHODS

The article provides a review of scientific results on the research of gene polymorphism that determine a body's response to the introduction of SARS-CoV-2 infection and the effects of pharmacotherapy for this disease, obtained from open and available sources within the period of 2019 – March 2021. The search was conducted in the following electronic databases: PubMed, Cochrane Library, ClinicalTrials.gov; Elibrary, Scopus. The main search inquiries were: "predictors + severe course + COVID-19", "genetic variations + COVID-19", "pharmacogenetics + COVID-19", "gene polymorphism + SARS-CoV-2", "pharmacotherapy + gene polymorphism + COVID-19" in both Russian and English.

RESULTS AND DISCUSSION

Genetic characteristics of human body response to establishment of SARS-CoV-2 infection

The genome-wide association search (GWAS) study where 8,582,968 single nucleotide polymorphisms were analyzed in 1,980 patients with severe COVID-19 in Italy and Spain has been widely publicized [5]. The control group included 2,205 healthy volunteers. According to the results of the study, no definite correlations were found between severe COVID-19 and the development of a respiratory failure and a single gene polymorphism. However, the determinants of a severe course associated with several genes have been identified. They are located in the fragment of chromosome 3 – locus 3p21.31, including the genes SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6 and XCR1. Among these genes, the following ones are distinguished as the most significant in the pathogenesis of the COVID-19 development: LZTFL1 (expressed in the lungs, it determines the production of the protein that regulates a ciliary function); SLC6A20 (the gene encoding the synthesis of the corresponding transporter protein involved in the transmembrane transport of sodium and chlorine ions, it also presumably affects the interaction between SARS-CoV-2 with ACE2 receptors); CCR9 (the gene encoding the synthesis of the membrane protein of the same name, is a part of G-protein-mediated receptors, and it is also a receptor for chemokines that control the migration of effector cells to the inflammation focus); CXCR6 (expressed in the lymphoid tissue and on activated T-lymphocytes, regulating their activity; including the effect on the immune response during inhalation of viral pathogens). The presence of the GA allele in the single nucleotide sequence rs11385942 was associated with a decrease in the CXCR6 expression and an increase in the SLC6A20 expression. According to the results of the meta-analysis, the occurrence frequency of the risk allele was approximately 1.5 times higher in the group of the hospitalized with a respiratory failure receiving a respiratory support compared with the group receiving only an oxygen inhalation (OR 1.77, 95% confidence interval 1, 48–2.11; $P=3.30\times10^{-4}$). Another result of this study was the establishment of the correlation between the severe course of the disease and the 9q34.2 locus, which, in this cohort of patients, determines a blood group according to the ABO system. A meta-analysis showed that the group of patients with an A blood type was 1.5 times more likely to have a severe course compared with the other blood types (OR 1.45; 95% CI, 1.20–1.75; $P=1.48\times10^{-4}$), and a protective effect was also found in the carriers of the 0 blood type (OR 0.65; 95% CI, 0.53–0.79; $P = 1.06\times10^{-5}$). More reliable data could be obtained if the control group included people with an asymptomatic form and a mild course of SARS-CoV-2 infection, and not healthy people who were not infected with this virus.

Angiotensin-converting enzyme and transmembrane serine protease

Another direction in the search for genetically determined predictors of severe COVID-19 is to study the interaction of SARS-CoV-2 with host cell proteins during the virus introduction into the human body, which may explain the differences in viral loads. The penetration of SARS-CoV-2 into the cell is realized with the help of surface S-proteins, which interact with type 2 angiotensin-converting enzyme (ACE 2) in the place with a protease activity. The virus infects epithelial cells of the respiratory and gastrointestinal tracts and a number of other organs. There is a high expression of ACE 2 by type II alveolar pneumocytes, which determines the tropism of SARS-CoV-2 to the lung tissue. To activate the viral S-protein, the TMPRSS2 enzyme is required. It facilitates the penetration of the virus into the host cell [7]. TMPRSS2 can be considered a potential therapeutic target in the COVID-19 treatment.

TMPRSS2 inhibitors currently used in Japan and approved for the treatment of several forms of prostate cancer and pancreatitis are potential candidates for the treatment of SARS-CoV infection [8]. The TMPRSS2 gene is localized on chromosome 21q22.3; its expression level is subject to genetic polymorphism, which can determine susceptibility, a viral load, and risks of severe lung damage in the SARS-CoV-2 infection [9]. Single nucleotide polymorphisms TMPRSS2 rs383510 and rs464397 showed the highest expression in the lungs of

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patients with homozygous TT genotype, rs2070788 – GG genotype and rs469390 with AA genotype. Accordingly, rs383510, rs464397 heterozygous CT genotype and rs469390 with AG genotype showed an intermediate level of TMPRSS2 expression, and homozygous CC genotype (rs383510, rs464397), GG (rs469390) and AG and AA genotypes (rs2070788) had the lowest expression. The prevalence of the TMPRSS2 genetic polymorphism differs in the population. For example, the population of East Asia has a lower frequency of genotypes with a high expression compared to the American and European communities [10].

After a high affinity connection of the virus with ACE 2, the fusion with the host cell occurs, the penetration into it and the multiplication of the virus. The synthesis of ACE 2 is associated with a polymorphism in the gene encoding this protein. A point mutation in the ACE 2 gene (Leu584Ala) increases the penetrating ability of SARSCoV-2. It is interesting to report that several amino acid sequences fundamentally alter the interaction between the viral S1 protein and the ACE 2 receptor, changing the viral load. A total of 13 polymorphisms (rs1434130600, RS1395878099, RS142984500, RS756231991, RS1244687367, RS73635825, RS778500138, RS867318181, RS763395248, rs4646116, rs778030746, rs1199100713 and rs781255386) determine the rapid and effective interaction of ACE 2/S1, which contributes to the development of the infection. In contrast, the other 18 SNPs (rs143936283, rs961360700, rs1569243690, RS751572714, RS1348114695, RS1263424292, RS766996587, RS760159085, RS1016409802, RS146676783, RS1352194082, rs755691167, rs1325542104, rs759579097, rs762890235, rs1192tnqh_9; 192618, rs370610075 and rs1256007252) impede the interaction between ACE 2 and S1, thereby reducing the level of infecting [11]. At the same time, a high activity of ACE 2 has a protective effect on the pulmonary function. The SARS-CoV-2 infection likely decreases the regulatory function of ACE 2. A decrease in the activity of ACE 2 triggered by the virus, and an increase in the level of angiotensin II because of it, leads to the synthesis of proinflammatory cytokines and chemokines through the interaction with the AGTR1 and AGTR2 receptors with a subsequent activation of NF-κB. This contributes to damaging the alveolocytes and endothelial cells, the development of interstitial edema and infiltration of the lung tissue [11].

Another gene that can potentially influence the COVID-19 severity, is AGTR2 which encodes Angiotensin II receptor Type2 (AGTR2). Thus, it can be assumed that it is binding of SARSCoV-2 with AGTR2 directly and / or indirectly through the ACE 2 receptor, that leads to the imbalance of the renin-angiotensin system, the excessive accumulation of angiotensin II and, as a consequence, to severer forms of the disease [12].

Dipeptidyl peptidase 4

Dipeptidyl peptidase 4 is an intramembrane glycoprotein and serine exopeptidase. This enzyme is involved in the degradation of a wide range of substrates, including chemokines, neuropeptides, and incretins (e.g., glucagon-like peptide-1). DPP4 is a surface antigen also known as CD26. DPP. It is expressed in many organs and tissues, including the lungs, intestines, placenta, kidneys, and immune cells. Previously, it was found that DPP4 plays a role in the priming of glycoprotein S at the moment of MERS-CoV penetration into host cells [13]; its role in the penetration of SARS-CoV-2 is currently being considered [14]. A single nucleotide polymorphism of the DPP4 gene (rs13015258 – C allele) was found, which is associated with a very high expression and increased mortality among COVID-19 patients with type 2 diabetes mellitus [9].

Toll-like receptors

One of the most important functions of innate immunity is the recognition of microbial components by cells. It determines the launch of the first line of human body defense against the pathogens invasion. TLRs play a key role in the recognition and activation of the immune response. In humans, 10 subtypes of these receptors have been identified, each of which is responsible for the identification of various structural components of microbes. The SARS-CoV-2 virus enters the cells, binds to the endosomal TLRs of types 3 and 7, and cytoplasmic RNA receptors. These structures play an essential role in the recognition of viral RNA and the initiation of interferon genesis as one of the main components of innate immunity and antiviral defense. The cascade of reactions occurs due to the activation of the NF-κB and IRF pathways. In the literature, there are limited data on a low expression of the X-chromosome gene encoding TLR7 synthesis, and, accordingly, a reduced activity of interferons (types I and II) which was accompanied by the development of severe COVID-19 in young men [15]. In addition to finding a genetic link that could open up all sorts of new opportunities for exploring potential treatments, this study can also explain the observed trend towards higher death rate from COVID-19 in men than in women. A number of genes and regulatory elements associated with the innate and adaptive immune response have been found in the X chromosome [16].

Interferon status

The synthesis of endogenous interferon is a universal evolutionarily fixed defense mechanism against

viral infection. Delayed stimulation of the expression of genes responsible for interferon genesis and antiviral response is associated with the severity of clinical manifestations of infectious diseases. In deceased patients with MERS-CoV infection, the level of the endogenous interferon synthesis was significantly lower than in survivors [17]. The activation of this pathway is associated with the induction of the expression of several hundred genes that affect the suppression of viral replication. Gene variations that determine the low functional activity of the type 1 interferon response are characterized by the development of immunodeficiency states and the life-threatening course of viral infections.

A number of works have demonstrated the relationship of severe COVID-19 with a low activity of this pathway. Having analyzed the genome of 659 patients with severe SARS-CoV-2 infection, Zang [18] identified 13 candidate genes responsible for the implementation of the type 1 interferon response. In 23 patients out of 659 (3.5%), mutations realized by reduced activation of the interferon pathway and characterized by a more severe course of the disease, had been found. These patients had a high viral load. Previously, it was shown that the single nucleotide polymorphism rs12252C / C in the IFITM3 gene (encodes the interferon-induced transmembrane protein 3) is a risk factor for severe influenza [19]; this polymorphism, rs12252C / C, was also found in a patient with severe COVID-19 [20].

Another possible cause for severe SARS-CoV-2 infection can be the production of neutralizing autoantibodies [21]. Autoantibodies aimed at blocking regulatory proteins, in particular INF-α and INF-ω, were found in 101 out of 987 patients (10.2%; 94% of which are mostly men over 65 years old) with life-threatening conditions in the current pandemic. The production of neutralizing autoantibodies correlated with low plasma concentrations of INF-α. In addition, autoantibodies to type 1 INF proteins were not detected in 663 patients with asymptomatic or mild COVID-19, and in the population of healthy individuals not infected with SARS-CoV-2, autoantibodies were detected in 0.33% of cases (4 / 1227 people). The production of autoantibodies to type 2 INF, IL-6 and IL-17 has been detected in healthy people, patients with autoimmune diseases and opportunistic infections, but their role in determining the severity of diseases is not yet fully understood [22]. The literature provides rare cases of hereditary conditions with an autoimmune mechanism or immunodeficiency, which were accompanied by overproduction or deficiency of type 1 interferon response proteins, respectively. However, some cases have been notified that in conventionally healthy people with a low expression of the genes that determine this response, a clinically asymptomatic carrier state of these genomic variations is possible until the moment of contact with certain viruses. This may explain the cause for the severe SARS-CoV-2 in the patients without a history of immunodeficiency in anamnesis [15]. The determination of autoantibodies to type 1-interferon response proteins can be useful in determining a therapeutic strategy for patient management. In the presence of autoantibodies, recombinant INF-β preparations will not be effective, and these patients should not be considered as plasma donors. If this is a variant with a low expression of genes responsible for type 1-interferon response, then, on the contrary, therapy with recombinant interferon preparations is advisable.

HLA system

The genes of the HLA (Human Leukocyte Antigen) major histocompatibility complex system encode molecules of the same name on the cell surface. These protein structures carry out the presentation of various antigens, including causative agents of viral infections, and determine the severity of many diseases. This is the most polymorphic human genetic system (more than 9000 alleles), and it is located on the short arm of chromosome 6 [23]. Considering the role of the HLA system in the formation of the immune response, polymorphism of the genes of the main histocompatibility complex can determine the predisposition and variants of the course for infectious diseases. Thus, it is known that a severer course of H1N1 influenza is associated with the genotypes HLA-A*11, HLA-B*35 and HLA-DRB1*10; and with HIV-1, carriers of HLA-A* 02: 05 have a reduced risk of seroconversion [24]. There is a theory that the HLA gene polymorphism was formed during epidemics of infectious diseases, with the selection of alleles with a different peptide-binding ability. Moreover, heterozygotes with different HLA molecules are more adapted to the formation of an immune response as compared to homozygotes [25]. In 2003, during the SARS-CoV epidemic, a correlation was shown between the HLA gene polymorphism and a severer course of infection in carriers of HLA-B * 46:01. Based on these data, an *in silico* analysis of the 145 HLA genotypes affinity for the protein structures of SARS-CoV-2 was performed [26]. It has been shown that the HLA-B*46:01 genotype has the lowest binding capacity for SARS-CoV-2 proteins, which may be a predictor of a severer course of this disease. A similar response was predicted for genotypes HLA-A*25:01 and HLA-C*01:02. In contrast, the genotypes HLA-B*15:03, HLA-A*02:02 and HLA-C*12:03 showed a high activity in the presentation of SARS-CoV-2 antigens, which suggests good protective immunity.

In another study, Tomita Y. et al. performed an *in silico* analysis based on the prevalence of HLA gene

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polymorphisms and associations of the most frequent alleles in the countries with high mortality rates from COVID-19 [27]. The authors found possible the associations between the HLA-A*02:01 genotype, which determines a relatively low binding capacity for SARS-CoV-2 antigens, compared to individuals with the HLA-A*11:01 or HLA-A*24:01 genotype developing a more efficient T-cell mediated antiviral response to infection. The most common HLA genotypes in humans around the world have been studied and it has been shown that the variants HLA-A*02:01, HLA-C*07:01, HLA-DPB1*04:01, HLA-DQPB1*03:01 are found in more than half of the world's population. Then 19 countries were selected and divided into two groups: the first – where these allelic variants are most often found, the second – with a low frequency of these genotypes. Then, a correlation analysis was carried out between the frequency of these genotypes prevalence and the total number of confirmed cases and deaths from COVID-19 per 1 million population. A carrier state of HLA-C, HLA-DPB1, HLA-DQPB1 genotypes did not show fundamental differences between the countries in terms of the analyzed indicators. At the same time, in the countries where the HLA-A*02:01 genotype was more common, there was a statistically significant higher incidence of COVID-19 (1842 cases / 1 million population dated April 24, 2020, and 5795/1 million population dated August 15, 2020) compared with the countries where the genotypes HLA-A*24:02 and HLA-A*11:01 prevailed (97 cases / 1 million population in April 2020, and 419 cases / 1 million population in August 2020), as well as the mortality – 98 vs. 2.5 cases in April 2020 and 488 vs. 6.1 cases in August 2020, respectively. To determine the risk group, the authors of the two presented studies propose to conduct HLA typing and COVID-19 testing, as well as to vaccinate primarily high-risk individuals in accordance with genetic research data simultaneously.

Cytokine status

Cytokines are low-molecular-weight proteins that are signaling molecules and through specific receptors carry out cooperation between different cells and systems under normal conditions, as well as in the event of pathological processes. Cytokines are key mediators of the inflammatory response and are important for protecting humans from a wide range of viruses, participating in the regulation of both the innate immune system and inflammatory processes. Individual cytokine levels are highly variable, and genetic factors contribute significantly to the personal profile. Numerous studies have shown that the polymorphisms in genes encoding cytokines can affect their transcriptional activity, and, accordingly, the level of production [28]. In some cases, when exposed to infectious pathogens, autoimmune mechanisms and neoplastic syndrome, hypercytokinemia, i.e. uncontrolled release of inflammatory mediators, which is accompanied by an immune dysfunction, a systemic inflammatory process with damage to its own tissues and the development of a multiple organ failure, is possible [29]. Among the possible stimuli for the initiation of a cytokine storm, the role of coronaviruses, and in particular SARS-CoV-2, has been established. In the COVID-19 patients and a cytokine storm signs, changes in the production of many cytokines have been established: IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IFN-γ, TNF-α and TGF-α β1. Among them, the most typical overproduction is of IL-6, IL-1β, IL-10 and TNFα. The role of genes polymorphism encoding a cytokine production had been proven for many infectious diseases, including malaria, influenza, meningococcal infection and sepsis in previous studies [30,31]. Considering that, variants of proinflammatory cytokine genes were also studied in SARS-CoV- 2 infections. However, none of the previously identified polymorphisms of proinflammatory cytokine genes associated with more severe diseases, have been replicated in COVID-19 studies. Thus, in a published case-control study in SARS-CoV patients, no relationship was found out between the course of the disease and the TNF-α gene polymorphism [32], and no correlation was found out between the COVID-19 severity and the genetic variants of this gene in 900 SARS-CoV-2 patients in a modern study. [33].

IL-6 is one of the pro-inflammatory cytokines, the level of which increases dramatically in COVID-19 patients [34]. In addition, its level is considered a severity predictor of this disease. Higher levels of circulating IL-6 are observed in patients with respiratory dysfunction, suggesting that SARS-CoV-2 triggers a cytokine-mediated mechanism of the lung injury; these patients were significantly more likely to have indications for respiratory support [35]. Genetic variations that determine the IL-6 production, are considered potential determinants of the host cell's response to the SARS-CoV-2 invasion [36]. The previous studies have shown that mutations in the IL-6 gene (rs1800797 and rs1800795) are associated with the progression of cardiovascular pathology [37]; and combined polymorphisms of the IL-6 (rs1800797), IL-10 (rs1800872) and C-reactive protein genes (rs1205) correlated with the severity and prognosis in the patients with community-acquired pneumonia [38]. However, among the data available for the analysis of the role of genetic predisposition to the synthesis of IL-6 in COVID-19, only one study showed that the carrier status of the IL-6 -174C allele is associated with a higher level of the IL-6 production and severer forms of pneumonia in general. This result does not reflect a direct relationship between the disease severity and the gene polymor-

phism, but confirms that IL-6 plays a key role in the progression of the novel coronavirus pneumonia [39]. Thus, more detailed information on the relationship between the polymorphism of cytokine genes that are important in SARS-CoV-2 infection, and the COVID-19 severity, requires further scientific research.

Pharmacogenetic markers of efficacy and safety of COVID-19 therapy

Genetic variations in COVID-19 patients can affect not only the nature of the infection course and the severity of clinical manifestations, but also determine the individual response to the pharmacological drugs used. This review provides data on the drugs recommended for the COVID-19 treatment and possible changes in the efficacy and safety of the therapy associated with patient gene polymorphisms. Although there are currently no data from pharmacogenetic studies in COVID-19patients, there are plausible mechanisms by which important genetic determinants can be anticipated.

Hydroxychloroquine

Hydroxychloroquine is an antimalarial 4-aminoquinoline derivative. Due to its anti-inflammatory and immunosuppressive action and in addition to the treatment and prevention of malaria, it is included in the clinical guidelines for pharmacotherapy of rheumatoid arthritis and systemic lupus erythematosus. Hydroxychloroquine is one of the first etiotropic drugs included in COVID-19 treatment protocols. The mechanism of the hydroxychloroquine antiviral action in COVID-19 is not yet clear. Presumably, the drug prevents the penetration of the virus into the cell, disrupting the processes of endocytosis. In addition, hydroxychloroquine can directly affect the interaction between SARS-CoV-2 and ACE 2 by reducing the glycosylation of ACE 2 [40]. The immunosuppressive effect is manifested by a decrease in the production of pro-inflammatory cytokines, which may also have a beneficial effect on the hyperimmune response in COVID-19. The efficacy and safety of hydroxychloroquine is related to the pharmacokinetics of the drug. The drug is metabolized in the liver by the CYP P450 system with the participation of the enzymes CYP2D6, CYP2C8, CYP1A1 and CYP3A4. The genetic polymorphisms of enzymes affect the metabolic rate and, accordingly, the pharmacological response. In the previous studies, alleles CYP2C8*2, CYP2C8*3, CYP2C8*4 reduced the activity and capacity of the enzymes *in vitro* compared to the wild-type CYP2C8*1A allele, which led to a delayed formation of active metabolites of the drug and a decrease in the therapeutic response [42]. CYP2D6 polymorphism (rs1135840 andrs1065852) induces the metabolism of hydroxychloroquine in a patient with systemic lupus erythematosus [41]. Single nucleotide polymorphisms of the gene encoding the synthesis of glucose-6-phosphate dehydrogenase (rs5030868, rs1050828, and rs1050829) are associated with a decrease in the enzyme activity and an increased risk of hemolysis [43].

Remdesivir

Remdesivir is an antiviral drug that is an adenosine nucleotide prodrug metabolized in the cells of the body to form an active metabolite of nucleoside triphosphate. Remdesivir triphosphate acts as an analogue of ATP and competes with the natural ATP substrate for incorporation into the forming RNA chains using the RNA-dependent RNA polymerase of the SARS-CoV-2 virus, which leads to a delayed chain termination during the viral RNA replication [44]. Remdesivir undergoes serial metabolism mediated by intracellular esterases and phosphoamidase, which leads to the formation of the main metabolite of remdesivir. Pharmacogenetic studies of remdesivir have not been published to date, but *in vitro* studies show that it is a substrate for the enzymes CYP2C8, CYP2D6, and CYP3A4, as well as a substrate for the transporters OATP1B1 and P-glycoprotein [45]. Thus, the known polymorphisms of these genes can theoretically influence the pharmacokinetics of remdesivir [46].

Favipiravir

Favipiravir was developed and approved in Japan, 2014, for the treatment and prevention of influenza and is currently being investigated for its effectiveness in COVID-19. There are no published studies on the pharmacogenetics of favipiravir. Possible ways of changing its efficacy may be associated with the competitive metabolism of the aldehyde oxidase pathway, which is the main pathway for its deactivation [47].

Interferon β-1b

The use of interferon preparations, in particular IFN-β1b, has manifested its efficacy in the treatment of SARS and / or MERS coronavirus infection, and is currently being studied in COVID-19 [48]. The changes in the efficacy and increased risk of the side effects of IFNβ-1b drugs associated with pharmacogenetic factors, have not been established. However, in the cohort of Swedish patients with multiple sclerosis who had received INF-β1b, the risk of developing biologically significant neutralizing antibodies was higher in the patients with the HLA-DRB1*04 allele (OR: 3.53, 95% CI: 1.64-7.61) and lower with HLA-DRB1 * 15 (OR: 0.33, 95% CI: 0.16–0.71) [49].

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Tocilizumab

Tocilizumab, an inhibitor of IL-6 receptors, is actively used as rheumatoid arthritis biological therapy. Considering the proven role of IL-6 overproduction in the pathogenesis of severe COVID-19, the use of drugs that block the effects of IL-6, is justified. Genetic biomarkers of the tocilizumab efficacy in rheumatoid arthritis, including variations FCGR3A, IL6R, CD69, GALNT1845–47, have been previously reported. 87 patients with rheumatoid arthritis treated with tocilizumab and FCGR3Ars396991TT genotype, showed a better response in 12 months (vs. GT; OR: 5.1; 95% CI: 1.2–21.3; p = 0.03). This variant can affect the affinity of the Fc-fragment of the IgG receptor for tocilizumab and alter its systemic clearance [50].

Now, there is limited evidence that pharmacogenomic biomarkers can help with determining the response to tocilizumab therapy in COVID-19, and the translation of these data into the course of COVID-19 is incorrect. There are no studies on the pharmacogenetics of tocilizumab in the patients with cytokine overproduction syndrome that could be close to the COVID-19 pathophysiology, either. Herewith, the identification of the response markers to tocilizumab in SARS-CoV-2 can make it possible to carry out individual targeted therapy and not to use immunosuppressants to treat a viral disease in a number of patients with predictors of a therapy failure. Another important aspect of the need for these studies is the economic factor.

Janus kinase inhibitors

Tofacitinib and baricitinib are other biologically active drugs that block the hypercytokine response and are approved for the use in COVID-19. Currently, no data on the pharmacogenetics of these drugs have been published. However, their pharmacokinetic parameters include several potentially important candidate genes. The both drugs are substrates for CYP3A4. Tofacitinib is also partially metabolized by CYP2C19. The both genes of metabolic enzymes are susceptible to genetic polymorphisms, which can alter the drugs activity [51].

Systemic glucocorticosteroids

Glucorticosteroids (GCS) are powerful nonspecific anti-inflammatory and immunosuppressive drugs. In the treatment of patients infected with COVID-19, they are used in the treatment of acute respiratory distress syndrome (ARDS). Pharmacogenetic predictors of the systemic corticosteroids effectiveness in ARDS have not been identified. However, possible variants of the pharmacological response may be associated with the receptor activity, as well as pharmacokinetic pathways through the activity of metabolic enzymes and transporter proteins [52]. GCS metabolism is carried out in the liver with the participation of isoenzymes CYP3A4 and CYP3A7, as well as in the lung tissue under the influence of CYP3A5 and CYP3A7 [53]. CYP3A4*22 polymorphism of the gene encoding CYP3A4 can change the activity of the isoenzyme and, accordingly, affect the therapy effectiveness. Thus, in previous studies, it was shown that in heterozygotes with the CYP3A4*22T(C/T) genotype, the effectiveness of glucocorticosteroid therapy was higher compared to the C/C genotype [54].

Another pharmacokinetic factor that can alter the efficacy and safety of glucocorticosteroid therapy is the expression of P-glycoprotein. Its level of activity is associated with genetic polymorphism of the multidrug resistance gene MDR1 (ABCB1), which can affect the therapeutic response [55]. The expression of glucocorticoid receptors is encoded by the NR3C1 gene. A number of scientific studies are devoted to the study of the polymorphism of this gene; about 40 gene variants are known that encode the synthesis of these receptors [56]. The individual variability may determine the efficacy and safety of glucocorticosteroid therapy [57]. In addition, the affinity of glucocorticoid receptors can be altered by proinflammatory cytokines, IL-1 and TNF-α [58], which can possibly be an effectiveness factor in the of COVID-19 therapy with these drugs.

CONCLUSION

Thanks to joint efforts and concerted actions in the struggle against the novel coronavirus infection, a global access to vaccines, modern diagnostics and effective medicines is ensured for all people who need them. However, the struggle against COVID-19 is going on. Scientific studies detailing the mechanisms of infection with SARS-CoV-2, the variability of the severity of the course of the disease and the individual characteristics of the therapeutic response to the drugs used, do not lose their relevance and have great social significance. The genetically determined heterogeneity of the immune response to SARS-CoV-2 requires further study, since there is no clear opinion about the leading mechanism that determines the severity of the disease. The results of studies on the search for genetic predictors of the disease severity and the effectiveness of COVID-19 pharmacotherapy, can form the basis for further search, as well as be used to develop strategies for preventing the infection, analyze potential targets of targeted therapy and develop protocols for optimizing this disease pharmacotherapy.

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Ivan N. Shishimorov – planning and editing the review; Olga V. Magnitskaya – material search and review editing; Yulia V. Ponomareva – material search and review writing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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