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CERTAIN APPROACHES WHILE CHOOSING THE STRATEGY OF COVID-19 PATHOGENETIC THERAPY AND IMMUNOPROPHYLAXIS

Avagyan S.A.[1]*, Muradyan A.A.[2], Zilfyan A.V.[1]

[1] Scientific Research Center, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia
[2] Department of Urology and Andrology, Yerevan State Medical University after M. Heratsi, Yerevan, Armenia

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Abstract

This report provides the authors' viewpoints on the prospects of carrying out several therapeutic and prophylactic measures aimed at least improving the health of patients suffering from COVID-19.

In addition, the authors have some doubts (fears) of using vaccines, the production of which is currently involved in well-known commercial pharmaceutical enterprises and scientific institutions of a number of leading countries of the world. At the same time, the authors place special emphasis on the scientific and technological process of vaccine production, when, as "initial raw materials", in each specific case, are used separate variations from the general structure of viruses pathogenic for humans, including SARS-CoV-19, integral killed coronaviruses, cross-reactive antibodies to SARS-CoV-19, which are obtained as a result of appropriate scientific and technological preparation of other viruses (for example, arboviruses).

How effective these vaccines will turn out to be is a matter of time, primarily due to their "approbation" on a wide contingent of people of different nationalities and living in different regions of the world.

According to the authors, the effectiveness of vaccines in many respects depends on the intensity degree and relatively long-term binding of specific antibodies to viruses, as well as on the results of active vaccination, especially since coronaviruses are characterized by a very wide variability of antigenic determinants, represented, in particular, by at least six antigen receptors.

The authors' doubts in this aspect served as a prerequisite for recommending new scientific and methodological approaches for COVID-19 treatment, based on the principles of suppressing the functional activity of SARS-CoV-2, both at the initial stages of binding the virus to the target cell membrane of the infected organism, and in the processes of their endocytosis, translation, replication and exocytosis of daughter viruses.

A detailed analysis of modern informative literary sources, as well as their own research, according to the authors, can serve as a real prerequisite for including α-difluoromethylornithine in the general treatment regimen for COVID-19 patients, a drug that selectively inhibits the initial stages of polyamine synthesis, thereby leading to significant suppression of SARS-CoV-2 biological activity in the infected organism.

Keywords: *coronavirus infection, pathogenetic therapy, COVID-19, SARS-CoV-2, polyamines, vaccination, α-difluoromethylornithine.*

Problems associated with the elimination of infectious diseases that are becoming epidemic and, especially, pandemic, have worried humanity since ancient times. The situation became even more complicated when viruses of the most diverse origins began to act as an etiological factor. Significant difficulties arose over many years, when bacterial pneumonia began to occur against the background of already developed viral pneumonia, and vice versa.

In both cases, mixed pneumonia, occurring, particularly on the background of resident microorganism translocation into the bronchopulmonary

Address for Correspondence:
Stepan A. Avagyan
Scientific Research Center
Yerevan State Medical University after M. Heratsi
2 Koryun Street, Yerevan 0025, Armenia
Tel.: (+374 93) 58-91-79
E-mail: namj.ysmu@gmail.com

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tissue, were accompanied by severe destructive and/or inflammatory processes that create significant difficulties in developing treatment strategies. In this situation, therapeutic interventions were generally aimed at suppressing regional (i.e., in situ) antibacterial activity directed against persistent pathogenic and opportunistic microflora both under conditions of microorganism infection and as a result of lung colonization by intestinal microflora. At the same time, antiviral therapy on the background of ongoing coinfection very often turned out to be ineffective.

So, when infected with type A virus, the influenza pandemic claimed many lives in many countries of the world. The sudden "epidemy" of HIV infection was also accompanied by huge human losses.

It should be noted that there was no "radical therapy" in both cases, not to mention immunoprophylaxis, since attempts to identify general and regional mechanisms of the pathological process were not always successful, taking into account the main etiological factor – pathogenic viruses persisting in human organism.

Despite the huge human losses as a result of even seasonal epidemics caused by type A influenza, humanity was very skeptical about the requirements of therapists and infectious disease specialists – to strictly adhere to known treatment and prevention regimens. Despite numerous losses, the main contingent of patients infected with type A influenza virus continued not to apply to the appropriate clinical and polyclinic institutions for medical assistance, adhering to the principle of self-healing "at home". In this case, fortunately, the majority of influenza infections, as they occurred, "spontaneously" came to naught. On the other hand, given the facts of "spontaneous" self-healing at the final stage of the influenza infection course, much less attention was paid to preventive tactics for the development of effective vaccines, which had a very negative impact on the treatment tactics of viral infections caused by other representatives of anthroponous and zoonotic viruses pathogenic for humans.

Immunoprophylaxis for HIV infection is also far from perfect.

Since 2002, infectious diseases caused by two members of the zoonotic family have become widespread among humanity (until the emergence of an epidemic): the coronaviruses of the severe acute respiratory syndrome (SARS-CoV) and the Middle East respiratory syndrome (MERS-CoV). Treatment of both coronavirus infections is mainly based on the use of remdesivir, which shows relative clinical efficacy. At the same time, throughout the entire "course of therapy" to this day there is a lack of additional antiviral drugs for effective treatment and prevention of these viral infections.

Practically the absence of clear schemes, directives or even recommendations had a very negative impact on the treatment and, first of all, on the immunoprophylaxis of the coronavirus infection COVID-19 that arose in 2019, which continued and continues to cover wide groups of the urban and rural population. The situation is more aggravated, since autopsy is practically "not recommended", which is fraught with the absence of a pathological diagnosis. At the same time, based only on clinical observations, including the latest laboratory researches, our knowledge regarding aspects of pathogenesis, including visceral disorders in COVID-19, is far from sufficient. In the treatment process the situation is significantly complicated by the fact that only lungs are the main damage "object", while immune, endocrine and metabolic disorders developing in many organs and tissues are very negatively reflected on the course of the regional inflammatory process (even at the very initial stages of the coronavirus pneumonia development). The question seems to be very controversial – to what extent, in the case of coronavirus infection COVID-19, the process of bacterial intestinal translocation of resident microorganisms can be involved in the organism infected with the virus, followed by the persistence of opportunistic and pathogenic microflora in new econiches of the macroorganism, and primarily in the bronchopulmonary tissue.

In connection with the severe course of COVID-19 and high mortality, the question naturally arises – to what extent modern epidemiology, as one of the fundamental dis-

To overcome it is possible, due to the uniting the knowledge and will of all doctors in the world

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ciplines of combating infectious diseases, in many countries of the world meets all the necessary requirements that must be presented to this discipline at all times. A similar situation is observed in the field of virology as well.

Modern communities in many countries of the world pin great hopes on obtaining effective vaccines, with the help of which it is possible to achieve success in the fight against the pandemic caused by COVID-19 in a relatively short time. Vaccination, as a way to effectively combat certain infectious diseases of viral etiology, at the beginning of the immunology development turned out to be quite an effective tool in the treatment and mass prevention of a number of viral diseases. As an illustrative example, it suffices to cite the chronological stage of development in immunology, which ultimately led to the production of an effective vaccine against smallpox. So, vaccination of smallpox, which has a rich ancient history, turned out to be very effective. For many centuries, in India, China, the countries of the ancient world, were used small portions of material from recovering people, which were applied to intact and affected skin areas of patients with smallpox. Little is known about the fact that variolation (from Latin smallpox) was relatively widespread in the East. This method was introduced to Europe in 1721 by the wife of the British ambassador in Istanbul, Lady Mary Montague. In Russia, Empress Catherine II was among the first to subject herself to variolation.

Edward Jenner, the world famous English physician, is considered the founder of vaccinology in the West in 1796. He proved the advantages of vaccination (from the Latin vaccinus, cow) over variolation, by inoculating a person with the vaccinia virus. Vaccination results for smallpox patients have exceeded all expectations. So, over the next two years after the discovery, 100,000 people were vaccinated with a high degree of effectiveness of the vaccine tested by Jenner. Unfortunately, the discovery of vaccination over the following years did not lead to the further development of the immunology of infectious diseases, since many aspects related to the production and testing of effective vaccines were very often ineffective.

As typical examples associated with infections of viral origin, it is enough to cite annotated information about the relatively low effectiveness of immunoprophylaxis for influenza and HIV infection.

Human influenza viruses belong to the Orthomyxoviridae family, which consists of the genera influenza A, B, and C virus. The type A virus was discovered in 1933 by W. Smith, S. Andrews and P. Laidlaw, the type B virus was discovered by T. Francis and R. Medgill in 1940, and the type C virus – by R. Taylor in 1949. Influenza A virus poses the greatest epidemic danger. Methods of active and passive immunoprophylaxis for type A influenza virus are characterized only by relative effectiveness and include human influenza immunoglobulin (passive immunization), as well as live and inactivated vaccines (active immunization). Unfortunately, vaccination is carried out only during periods of greatest risk of regional outbreaks of epidemics. With a preventive purpose, when a very wide contingent of people is encompassed in a specific seasonal period of the risk of influenza infection, total vaccination is often not carried out. The use of killed vaccines requires an annual revaccination: their effectiveness, unfortunately, does not exceed 60-70%. The often observed antigenic variations of the causative agent of influenza have a very negative effect on active and passive immunoprophylaxis.

Infection with the well-known anthroponosis – human immunodeficiency virus (HIV) aused significant human losses. Acquired immunodeficiency syndrome (AIDS) is a consequence of HIV infection. For the first time, HIV was identified by the French virologist L. Montenier in 1983 under the name LAV (from English – lymphadenopathy associated virus), and the American virologist R. Gallo in 1984 under the name HTLV-III virus (human T-lymphotropic virus type III). After establishing the identity, instead of two designations, the virus began to appear under the general name – HIV (from English – human immunodeficiency virus), or HIV. Currently, over 30 million HIV-infected people are registered in the world. Unfortunately, to this day, there is no effective pathogenetic therapy (chemotherapy). As a rule, drugs that suppress the activity of reverse transcriptase are used: zidovudine, azidothymidine, zalcitabine, didanosine, stavudine. Drugs of the antiviral activity spectrum (or their combinations) – the so-called immunomodulators, including those from the group of interferons, continue to be tested.

Numerous attempts to develop effective vaccines against HIV have not been crowned with

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success to this day. Attenuated live vaccines from recombinant strains, as well as killed and subunit vaccines, also continue to be tested. From the given specific examples, it becomes obvious how topical the problem of preparing effective vaccines against the emerging infectious process of viral etiology looks like. The problem in its totality is largely due to the often lack of a clear classification of viruses pathogenic for humans, taxonomic characteristics, the vagueness of such a concept as "bacteriophage", a noticeable lag of modern concepts in virology, stereotypical concepts such as transcription, translation, replication, which are mistakenly considered in generalized "schemes" exclusively for all viruses pathogenic for humans. As mentioned above, the situation is noticeably aggravated by the fact that systemic and organ disorders are extremely insufficiently studied. Subjective reasons mainly lie in our extremely poor knowledge of virology and in the absence of a single "directive concept" for the prevention and treatment of many viral infectious diseases.

In this aspect, infectious diseases of coronavirus origin are not an exception. In this regard, it should be noted that a number of advanced scientists are undertaking (not without success) an attempt to elucidate the pathogenesis, followed by correction of the pathological process in the lungs in pneumonia caused by known coronaviruses pathogenic for humans [*Mounce B et al., 2016 a,b; 2017; Firpo M et al., 2020 a,b*].

Since 2002, some coronaviruses pathogenic for humans have been the source of epidemic outbreaks, causing serious damage to the health of a wide contingent of people in many countries of the world. So, in 2002, there was an outbreak of severe respiratory syndrome coronavirus (SARS-CoV), since 2011 – an outbreak of Middle East respiratory syndrome (MERS-CoV), and from 2019 up to now – the most severe coronavirus infection – SARS-CoV-2.

As far as is known, in from 2002 up to now, the analyzed sources there is only separate information regarding aspects of immunoprophylaxis (including the use of vaccines) of acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV).

Despite the high level of development of many civilized countries (not to mention the backward and developing ones), the population of these countries, regardless of their intellectual levels of development, national characteristics and traditions, was very reckless and continues to relate to the observance of preventive (including isolation) measures, which led to the "total" spread of infection in many countries of the world in the form of the SARS-CoV-2 pandemic.

Meanwhile, the isolation of a wide contingent of infected patients, especially in the emergence of especially dangerous infections, was very recklessly rejected even in ancient times and the Middle Ages. A typical example, when a huge contingent of people infected with the plague, instead of being isolated, "sat down at a common refectory table", "anticipating" a tragic end for all. Until now, in our modern life, the concept "a feast in time of plague" is actual. In those distant times, only in small Montenegro, quarantine was involved, with the isolation of plague patients for forty days. At the same time, even in ancient times, a "prophylactic" method of isolating lepromatous patients was used by isolating them in the so-called leprosary. So, in history, there is information regarding the isolation of patients suffering from leprosy in ancient Armenia, when leprosary was often arranged at pagan temples. As an example is given a leper colony opened near the Arbenut springs in 260-270 AD by the wife of the Armenian feudal lord Suren Salauni, princess Agvid. The leper colony originally placed thirty-five lepers. In this regard, I would like to inform you that the first leper colony in Western Europe was opened in St. Claude in 570 AD, i.e. 300 years after the opening of the first leper colony in Armenia [*Hovhannisyan L, 1946*].

However, the existing centuries-old experience based on the preventive principle, unfortunately, in the context of COVID-19 infection, in the 21st century was ignored with a large degree of unjustified negligence, ignorance and pessimism, which led to the fact that the coronavirus-19 infection acquired a pandemic character with a high mortality rate.

The problem of creating effective vaccines against COVID-19, which, according to the media and agitation, is widely developed in a number of developed countries of the world: Russia, China, USA, England, Germany, France, etc., seems to be very urgent today.

Currently, 213 vaccines are at various stages of

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biotesting and commercial preparation, 66 of which are in clinical trials, and 9 are still undergoing large-scale randomized control [*Milken Institute, 2020; Soegiarto G, 2020*].

The vaccine development process is phased, and in general, is identical to the register of scientific and clinical trials, during their approbation in all countries of the world. This process is based on the principles of progressive implementation of the following stages (phases): preclinical, clinical and post- licensing.

We did not find it expedient to outline the specific criteria-parameters of each stage (phase), since all these three phases in the development of various vaccines are presented in a very detailed and accessible form for the reader in a scientific review article by Soegiarto G. (2020).

If the problem of developing antiviral vaccines is taken very seriously, then this process, including its permissive stage – obtaining a license, usually takes from 10 to 30 years [*Preiss S et al., 2016; CPP, 2020*].

In our particular case, i.e. in the context of the pandemic caused by SARS-CoV-2, the terms of test completion, and moreover, obtaining commercial vaccines is extremely limited, which, to a certain extent, is associated with high rate of COVID-19 mortality in many countries of the world.

As a result of such (very doubtful in our opinion) approach, vaccines obtained in a number of countries are not always effective, since in the conditions of "accelerated" vaccine production, researchers immediately go to clinical trials, without preliminary pre-clinical stage, or as a result of simultaneous pre-clinical and clinical trials (i.e. without waiting for the results of preclinical studies).

In this regard, as Soegiarto G. (2020) rightly points out, "researchers and health organizations should pay attention to the fact that clinical trials should not violate the Declaration of Helsinki, despite the urgent context of vaccine development [*WMA, 2018*].

Currently, in a number of countries, various platforms are used in the process of preparing vaccines, which have varying degrees of immunological activity and relative safety [*Milken Institute, 2020*].

Vaccine preparation has a long history and is generally based on active immunization methods. Passive immunization techniques have also been used over the years.

Relative detailed characteristics of vaccine preparation against COVID-19, their clinical (immunogenic) characteristics, countries and manufacturing companies are presented in a review article published in the "New Armenian Medical Journal" by Soegiarto G. (2020).

So, among the vaccines that are at various phases-stages of approbation (preclinical, clinical and production), are the following:

Vaccines prepared on the basis of a live and inactivated virus (attenuated and inactivated viruses). Attenuation of a live virus is carried out by introducing mutations in key virulence factors, and virus inactivation can be caused by radiation, heat treatment or chemical sterilization [*Kaur S, Gupta Y, 2020; van Riel D, de Wit E, 2020*]. One of the disadvantages of this is incomplete compliance of SARS requirements with safety level 3 [*Mauss S et al., 2014; Milken Institute, 2020; Netea M et al., 2020*].

Protein-based vaccines, consisting of purified proteins obtained from the virus and cells that are infected with the virus, as well as recombinant cells expressing the viral protein.

Vaccines in which a recombinant virus containing virus vector-based vaccine is used. In this case, the virus that is used as a vector can be replicative or non-replicative.

Vaccines prepared in the technology process based on DNA and RNA (DNA and RNA based vaccine). The DNA and RNA of the necessary antigen are introduced into the host cells, as a result of which the host cell's gene expression apparatus begins to express the antigen that elicits an immune response. Vaccines prepared on the basis of mRNA are expressed much faster (in contrast to DNA vaccines), since they do not require "crossing" the nuclear envelope.

Vaccines prepared on the use of antigen-presenting cells – APC (antigen presenting cell based vaccine). This platform does not apply to COVID-19, as it takes much longer to develop effective immunity than with other vaccines.

Passive immunization, adoptive immunity. In the clinic, "convalescent plasma therapy" is applied using sera from patients who have recovered from COVID-19, which contain polyclonal antibodies, especially directed to several natural epitopes of SARS-CoV-2. The therapy effectiveness largely depends on the properties of the most ad-

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ministered antibodies, which are very variable in different recovering patients.

Thus, it is not always possible to achieve exhaustive neutralization of SARS-CoV-2 with administered antibodies, opsonization of the circulating virus in blood, and acceleration of infected cell clearance. The disadvantages of passive immunization include the lack of control or randomization of study subjects. That is why it is necessary to conduct further research with a more objective assessment of the effectiveness of approved vaccines, especially in the phase of clinical trials [*Yan X, 2020*].

In general, most of the approved vaccines have a relatively low degree of immunogenicity, which requires repeated vaccinations [*Li X et al., 2020; Milken Institute, 2020*].

Against this background, each vaccine exhibited "undesirable side effects" characteristic only of itself, including: the risk of infection, spontaneous recombination and mutation, the possibility of carcinogenesis due to the inclusion of vector DNA, and a high level of threat to biosafety during production.

At present, in a number of countries of the near and far abroad, it is recommended to use at least three vaccines – "Sputnik", "Astra-Zeneka" and "Can Sino Bilogics", produced by the Research Institute of Epidemiology and Microbiology named after N.F. Gamaleya (Russia), Oxford University (UK) and Beijing University of Biology (China). All three vaccines are in phase III clinical trials. In all cases, a non-replicating viral vector was used, which guarantees high safety during the production process and less side effect than in cases of using a replicating viral vector. In all three cases, a lower degree of immunogenicity was stated than with a replicating viral vector, as a result of which it may be necessary, at least, to re-inoculate, i.e. revaccination.

At the same time, any approved viral vaccine can be endowed with the ability to induce a high level of neutralizing antibodies, which can cause the so-called antibody-dependent enhancement (ADE), as in the cases of vaccines against Dengue and SARS-CoV [*Bhopal S, Nielsen M, 2020; Su S et al., 2020*].

The principle of antibody-dependent enhancement (ADE) is based on the following. In cases of weak neutralizing antibody binding, the virus continues to reproduce, since the stage of involving macrophages and microphages into the immune process, which are not able to completely lyse (inactivate) phagocytosed viruses, seems to be ambiguous.

As a result of the above situation, due to a significant increase of the viral titer in cells and body fluids, there is a significant deterioration in the clinical picture of infected patients [*Soegiarto G, 2020*]. In this case, the immunological status is characterized by a significant activation of immune mediators, mainly of the proinflammatory action spectrum, which is referred to as a "cytokine storm", against the background of an imbalance of helper and killer subpopulations of lymphocytes [*Khandia R et al., 2018; Zaichuk T et al., 2020*].

In our opinion, there is a no less significant threat when, in case of incomplete phagocytosis, as a result of viral persistence in macrophages, changes in their virulent (including immune) properties can occur, as well as the ability to re-produce daughter viruses. What new immunogenic qualities SARS-CoV-2 can acquire in the processes of impaired nonspecific and specific immunological resistance of an infected organism, as well as its "completed" mutation, is a big question. In this regard, we consider it necessary to emphasize once again the circumstance that the mechanisms which are interested in the induction of a "cytokine storm" seem to be very diffuse (if not vague) today. All of the above facts, of course, cannot but affect the effectiveness of the approved and already applied vaccines (in the clinic) against COVID-19.

Currently, the subjects of special discussion are the possible immune mechanisms that are triggered in the organisms of SARS-CoV-2 infected patients during vaccination. For the most part, studies in this direction are based on the established fact, according to which the S-protein of SARS-CoV-2 has pronounced antigenic potencies. This feature of S protein localized in the viral spike has been successfully used in the vaccine development in which S protein is used as the antigen. In general, the main immunological exploration studies are based on the immunogenic properties of SARS-CoV-2 S-protein. At the same time, it should be specially noted that the same S-protein acts as a fundamental factor through which SARS-CoV-2 infects target cells of the host organism, with all the ensuing consequences: endocytosis, translation, replication of daughter viruses, their exocytosis, which ultimately leads to the death of the virus-sensitive cell. The immunogenic properties of SARS-CoV-2 are charac-

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terized by inhibition of a number of immune responses, characterizing, inter alia, suppression of innate and adaptive immunity, which is expressed in a relatively low level of antibody-producing plasma cells, a decrease in the activity of T-killer and Th1 subpopulations [*Duan L et al., 2020; Jeyanathen M et al., 2020; Poland G et al., 2020*].

At present, in the form of an established "dogma", dominates the concept, according to which SARS-CoV-2 begins to infect the target cell through a single receptor mechanism, due to the interaction of the binding domain of the viral spike (S) protein with angiotensin converting enzyme-2 (ACE- 2).

In our opinion, this is far from the only receptor mechanism that SARS-CoV-2 is possibly endowed with, and, moreover, not the only mechanism by which SARS-CoV-2 can infect target cells of a macroorganism. Thus, it is generally accepted that ACE-2 transforms angiotensin II, which has a pronounced vasoconstrictor action spectrum, into angiotensin 1-7, which, on the contrary, is a potent vasodilator [*Sugihartono T et al., 2020*].

At the same time, it was found that SARS-CoV can penetrate into target cells by binding to ACE-2 as a receptor [*Du L et al., 2009*].

It should be particularly noted that SARS-CoV and SARS-CoV-2 have a certain structural identity. Thus, the genomic sequence of SARS-CoV and SARS-CoV-2 is almost identical. However, mutations appeared in the viral spike, which appeared in November 2019, as a result of which a large contingent of people were infected around the world [*Angeletti S et al., 2020; Sugiharto T et al., 2020*].

Moreover, the SARS-CoV-2 spike protein is 76.5% homologous in amino acid sequences to the SARS-CoV spike protein. Many host cell infection mechanisms for both coronaviruses are mostly identical [*Xu X et al., 2020b*].

The angiotensin-converting enzyme is involved in a receptor mechanism in the cells of many organs and tissues. Of course, this is an evolutionarily formed mechanism of a balanced interaction of the above-named vasoconstrictor and vasodilator, with the aim of regulating blood pressure at all levels of the body integrative systems. That is why, even taking into account the fact that ACE-2 in COVID-19 may have a potential cross-reactive interaction with both angiotensin II and SARS-CoV-2, this possible mechanism in COVID-19, in our opinion, should not to be considered as the only one, moreover, decisive. Of course, in the near future, new, more "specific" mechanisms of the receptor interaction of SARS-CoV-2 with target cells of an infected organism will be discovered.

In this regard, it is enough to bring one illustrative example, according to which until recently it was believed that CD-147 also interacts by the receptor mechanism with SARS-CoV-2 [*Zhou Y et al., 2020*] But this "phenomenon" was rejected based on a number of fundamental studies [*Leonardi A et al., 2020; Shilts J et al., 2021*].

At the same time, it is considered established that CD-147 acts as one of the receptors localized on the surface of erythrocytes.

In our studies [*Zilfyan A et al., 2021*], we made an assumption that the erythrocytes of SARS-CoV-2 infected patients should be considered as possible sources of "delivery" of polyamines into the nucleocapsid of RNA-positive viruses for the purpose of packaging genetic material. The activation of the translation and replication processes of viruses in target cells is also not excluded. Unfortunately, polyamine-dependent CD-147 receptor mechanisms associated with the transport function of erythrocytes have not been the subject of special studies in the infectious process caused by a number of viruses pathogenic for humans, including SARS-CoV-2. In our opinion, it is possible that in the polyamine transport process and due to the presence of the CD-147 receptor on the surface of erythrocytes, under COVID-19 conditions a similar receptor mechanism is involved, based on binding SARS-CoV-2 to CD-147 (Basigin). The receptor mechanism also functions, in our opinion, due to the targeted "consumption" of polyamines localized in the cytoplasm of erythrocytes by SARS-CoV-2.

As can be seen from above, in different countries of the world, in each specific case, as a result of scientific research and in the process of commercial production, vaccines have been obtained based on completely different scientific and methodological approaches. Such a "bouquet" of vaccines with a multidirectional action spectrum is unlikely to be effective, since in the same country may arise a situation when, due to the relative ineffectiveness of using one commercial vaccine and replacing it with another, there is no effectiveness guarantee of the latter, not to mention possible

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changes in the structural and functional activity of coronaviruses persisting in the macroorganism. During the vaccination process, it is possible that new strains of the same coronavirus may appear in the macroorganism. How effectively antibodies, obtained as a result of vaccination, will react to new "transformed" forms of coronavirus-19, is also an urgent question. And finally, a "mixed" viral infection cannot be ruled out, for example, the combination of COVID-19 with various strains of influenza infection.

Clinicians should be worried about the fact that there is no guarantee – how complicated the situation can be if, in COVID-19, an influenza infection can join, or vice versa? How competent is the immune system for such a viral coinfection, or more precisely, adequately respond simultaneously to SARS-CoV-2 and influenza A virus, especially since their antigenic determinants are highly heterogeneous in relation to each other – in terms of production, at least specific antibodies. It is not clear at all what the possible picture of structural changes in the lungs and the character of "visceral" lesions is against the background of a similar viral co-infection, not to mention the possible startup of the process of bacterial translocation of intestinal resident microflora into new econiches of the macroorganism, primarily, into the lungs. In this situation, in our opinion, a situation of "functional overstrain of the immune system" may arise, with the threat of the emergence of active immunological tolerance in relation to specific viral and bacterial antigens.

We considered it appropriate to give an optimistic (predictive) view of the COVID-19 problem by the Indonesian scientist Soegiarto G., which we cite: "As COVID-19 continues to be a global threat, a safe and effective vaccine can be one of the greatest weapons to finally end this pandemic. However, many uncertainties about the efficacy, safety, equitability, and public acceptance of the vaccine remain. With the development of many vaccines entering phase III, we hope that these uncertainties will be answered satisfactorily" [*Soegiarto G, 2020*].

Moreover, the infectious process induced by SARS-CoV-2 is in dire need of further correct versatile studies, both immunological, hematological and endocrinological, especially since SARS-CoV-2 is an RNA-positive virus, which, unfortunately, is endowed with antigenic receptor variability and a tendency to mutation.

Unfortunately, specialists haven't used an alternative way to combat COVID-19, based on the search for effective means that prevent the main stages of the virus biological activity in the host organism during its direct contact with the target cell and in the process of penetrating into the virus-sensitive cells.

As an effective means of endogenous and of exogenous origin, stimulating the functional activity of several human pathogenic viruses, including some coronaviruses, aliphatic polyamines appear: putrescine, spermidine and spermine [*Mounce B et al., 2016 a,b; 2017; Firpo M et al., 2020*].

The role of the aforementioned polyamines in the vital activity of exclusively all cellular populations of the mammalian body has been known for a long time and, in general, includes the coordination of many processes by them, realized by intermediator intracellular interaction of the processes of repair, proliferation and apoptosis [*Gerner E, Meyskens F, 2004; Pegg A, 2009; 2016; Wallace H, 2009; Igarashi K, Kashiwagi K, 2010; Avagyan S et al., 2020*].

At the same time, as noted above, the same aliphatic polyamines play an essential role, which is assigned to the fundamental functions of coronaviruses in the infected organism.

In our studies, we expressed a point of view (claiming to a certain extent a hypothesis) according to which, as cellular polyamines are consumed, some viruses pathogenic for humans begin to "utilize" polyamines localized in resident opportunistic microorganisms during their bacterial translocation, from colonization of new econiches of the macroorganism and, first of all, of the lungs.

The special need for a number of human pathogenic viruses in polyamines dictates the need to find effective polyamine blocking agents, which will be an attempt to noticeably reduce the activity of coronaviruses at all stages of their contact with target cells, from adhesion on the cell surface to a possible polyamine-dependent inhibition of the intracellular processes of their translation and replication.

It should be especially noted that the use of α-difluoromethylornithine (DFMO) has proven to be relatively effective in the general register of a number of somatic diseases, which is also reflected in our monographs published over the past 2 years:

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"Polyamines and synucleins in the diagnosis and pathogenesis of neurological and oncological diseases [*Avagyan S, ZIlfyan A, 2020*].

"The new doctrine of extracerebral autonomous mechanisms of intersystem regulation (own concept) [*Zilfyan A, 2021*].

It is these publications that also touched numerous aspects regarding the biological role of aliphatic polyamines and their impaired metabolism in a number of oncological and neurological diseases. Information is also provided, according to which DFMO has been successfully tested over a number of years in a wide range of benign and, especially, malignant oncological diseases.

It is established that ornithine decarboxylase (ODC) in mammals acts as the only "trigger" enzyme for the formation of putrescine from ornithine.

That is why, more effective were those studies aimed at finding new effective means in practical oncology directed at inhibiting the activity of ODC [*Metcalf B et al., 1998*]. The most effective blocker of this class of drugs is the "irreversible" ODC inhibitor – α-difluoromethylornithine (DFMO) [*Meyskens F, Gerner E, 1999*].

Thirty years of experience in DFMO approbation served as a prerequisite for conducting exploratory survey in oncology, with the development of polyamine analogs that should compete with endogenous polyamines (putrescine, spermidine, and spermine) by inhibiting the activity and biosynthesis of ODC [*Wallace H, 2009*]. With regard to the DFMO therapeutic efficacy in the "treatment" of cervical intraepithelial neoplasia, of considerable interest, in our opinion, are the studies in which the DFMO effect on the expression of epidermal growth factor, which is known to be considered as a marker of the progression of cervical intraepithelial neoplasia [*Boiko J et al., 1998*]. Study results show that in the normal (control) epithelium, the localization of epidermal growth factor is limited to the basal layer of the epidermis, while in cervical intraepithelial neoplasia, the expression of epidermal growth factor was more widespread and began to cover more superficial layers of the epidermis. The therapeutic use of DFMO in cervical intraepithelial neoplasia significantly limited the spread of epithelial receptors for epidermal growth factor. This allowed the authors to conclude that disease progression is associated with spatial dysregulation of epidermal growth factor, which can be reversed by the use of DFMO. A noticeable therapeutic efficacy of DFMO was also established in studies of a number of authors [*Mitchell M et al., 1998*], when conducting complex therapy of patients with grade III cervical intraepithelial neoplasia. The use of DFMO was accompanied by a decrease in the tissue index of spermidine/spermine and an increase in the level of ornithine in blood plasma of patients suffering from cervical neoplasia.

As noted by the authors, the therapeutic use of DFMO (in various increasing doses) did not cause toxic disorders in patients with grade III cervical neoplasia. The effectiveness of using DFMO was also established in the complex treatment of multiple adenomas, which significantly prevented the risk of colorectal neoplasia [*Laukaitis C et al., 2011*]. Greater attention should be given to the scientific development, in which, on the basis of previously conducted experimental and clinical (including our own) studies, aspects related to the use of DFMO specific doses in the complex therapy of neuroblastoma in children are discussed [*Bassiri H et al., 2015*]. It is very noteworthy that symptomatic and pathogenetic therapy of a number of oncological diseases is carried out due to the increasing use of endogenously active substances, or their synthetic analogs. Since it is endogenous biological factors that, in conditions of their disturbed metabolism in situ, largely determine the nature and characteristics of the course of many oncological diseases.

We deliberately dwelt in some detail on the established DFMO efficacy in oncological diseases, which was analyzed on specific examples. In many studied benign and malignant neoplasms, in tumor cells, as a rule, were recorded high levels of aliphatic polyamines: putrescine, spermidine, spermine.

In our opinion, considering the numerous functions of aliphatic polyamines in the mammalian organism, in particular the coordination of a balanced provision of proliferative processes, high levels of polyamines in tumor cells, in addition to other provoking factors, provide a sharp increase in proliferative reactions, which is also fraught with the appearance of anaplastic processes. Apparently, in this particular case, the evolutionarily fixed mechanism is upset, based on the balanced coordination of intracellular apoptotic and proliferative processes, which are caused by polyamines.

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As we indicated earlier, at present, the aspects concerning the role of aliphatic polyamines in a number of infectious diseases caused by viruses pathogenic for humans are the subject of wide discussion. And COVID-19 is no exception.

In this regard, it is necessary, in our opinion, to pay attention to the following circumstance. So, despite the development of large-scale research in order to obtain effective vaccines against SARS-CoV-2, unfortunately, the "alternative way" dropped out of sight of specialists, based on the search for effective means that prevents the main stages of the virus biological activity in its direct contact with the target cell and in the process of penetration into the virus-sensitive cells. We are talking about the following chronological stages in the process of contact of the virus with the target cell: attachment of the virus to the cell membrane, endocytosis, start of translation and replication processes, exocytosis of daughter viruses.

Some RNA-positive viruses pathogenic for humans, in order to realize their functions in mammals, require aliphatic polyamines, which facilitate the attachment of viruses to the surface of the target cell, and the processes of translation and replication are realized [*Mounce B et al., 2016 a,b; 2017; Firpo M et al., 2020*]. It is very noteworthy that in the nucleocapsid of some viruses pathogenic for humans, including coronaviruses, there are specific representatives of aliphatic polyamines, due to which their genetic material is packed.

Of certain, partly historical, interest is the fact that actually "the critical systems in which the role of polyamines in viral infection was first established were bacteriophages". Of great interest is the fact that packaging of DNA and RNA bacteriophages into virions occurs due to polyamines [*Dion A, Cohen S, 1972 a,b*]. For example, putrescine and spermine were found in bacteriophage R-17 [*Ames B et al., 1958; Fukume J, Cohen S, 1975; Cohen S, Mc Cormick F, 1979*]. In another bacteriophage, T4, the content of polyamines is influenced by the growth conditions of E. coli. According to Firpo M. and co-authors (2020), using the example of bacteriophage T4, apparently involves a stereotypical mechanism of the inclusion of polyamines in the virion. At the same time, the inclusion of polyamines in the virion largely depends on the metabolic situation of the infected cell, depending on the conditions of its residence. Thus, in particular, bacteriophage T4, isolated under anaerobic conditions, contained cadaverine, one of the representatives of the polyamine group. In some bacteriophages, as a result of infection with E. coli, endowed with different functional activity, under conditions of polyamine deficiency, it was found that polyamines play a certain role in phage translation [*Young D, Srinivasan P, 1974*]. Another bacteriophage – R-17, is characterized by the accumulation of spermidine in the infected cell – E. Coli [*Fukuma J, Cohen S, 1973; Fukuma J, 1975*].

According to Firpo M. and Mounce B. (2020) "polyamines are critical receptors in prokaryotes, and later studies soon have demonstrated a role for polyamines in eukaryotic viruses".

Even in individual examples (RNA-positive viruses and bacteriophages), in our opinion, it becomes obvious that the functional activity of some RNA-positive viruses pathogenic for humans largely depends on the presence of specific representatives from the group of polyamines (and not all of them in its entirety) in nucleocapsids.

With the depletion of intraviral polyamines, including those localized in supercapsids, viruses begin to "utilize" polyamines localized in the target cells of the macroorganism. Apparently, a similar mechanism in a number of viral infections seems to be a necessary condition for the progression of the pathological process in the bronchopulmonary tissue. With the depletion of intracellular polyamines, in our opinion, resident opportunistic microorganisms rich in polyamines begin to act as sources of "utilization" of polyamines, entering the infected lungs from their biological econiches (from the gastrointestinal tract and oral cavity), due to bacterial translocation.

The mechanisms underlying the peculiarities of polyamine metabolism in a number of oncological diseases and some viral infections pathogenic for humans, in our opinion, have a number of common features associated mainly with the activation of genetic mechanisms responsible for the synthesis of nucleic acids, the processes of transcription and translation, which ultimately lead to the steady multiplication of the macroorganism cells in the first case and the reproduction of daughter viruses in the second.

In our opinion, in both cases, the general prin-

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ciple of polyamine-dependent mechanisms is involved, due to the activation of proliferative processes both in tumor cells, which ensure their steady growth, and in the viruses themselves, due to their unique ability to utilize polyamines from target cells in order to provide intracellular functional activity, which ultimately leads to intensive multiplication of daughter viruses – replication.

The special need for a number of human pathogenic viruses in polyamines dictates the need to find effective polyamine blocking agents, due to which an attempt will be made to noticeably reduce the activity of coronaviruses at all stages of contact with target cells: starting with weakening of adhesion on the cell surface and ending with a possible polyamine-dependent inhibition of the intracellular processes of their translation and replication. According to a number of authors [*Firpo M et al., 2020*], tactics that pursue the goal of depleting the reserves of polyamines in the infected organism is "a strategic approach, since it is aimed at a relative weakening of the viral infection course in the mammalian body".

The search for effective agents that suppress the synthesis of polyamines in coronavirus infection was aimed at inhibiting key enzymes that are directly involved in the general cascade of reactions responsible for the stepwise synthesis of aliphatic polyamines: ornithine decarboxylase and adenosylmethionine decarboxylase [*Stanek J et al., 1992; Seiler N 2003; Mounce B et al., 2016 a,b; Firpo M et al., 2020*].

In this regard, according to a number of authors [*Firpo M et al., 2020*], the use of α-difluoromethylornithine (DFMO) turned out to be the most effective in the treatment of certain viral infections, including those caused by certain coronaviruses that are pathogenic for humans, but not COVID-19.

Under in vitro conditions, the authors have shown that DFMO treatment leads to a significant decrease in polyamine levels (depending on time and dose) in many cells. Moreover, DFMO suppresses the infection of cells by some viruses, both in vitro and in vivo. In this regard, the results on using DFMO in some mixed viral-fungal and pneumociystis carini infected pneumonia, characterized by a p particularly severe course of the pathological process in the lungs are relatively encouraging [*Pfaller M et al., 1988; Meralii S, Clarkson A, 1996*].

Apparently, DFMO has a pluripotent action spectrum, blocking the synthesis of polyamines at various stages of the interaction of viruses with macroorganism cells, including the processes of translation and reproduction of daughter viruses (replication).

In a recent publication of Firpo M. Mounce B (2020), the authors provided very informative data, according to which, in a number of viral infections, DFMO blocks the virus adhesion to the target cell membrane. According to the authors, this process is due to the "deficiency" of polyamines, which are given an important role in the "facilitation" of the virus adhesion to virus-sensitive cells in the infected organism.

In addition to enzymes that block polyamine production at the earliest stages of the synthesis of putrescine from ornithine, some pharmaceutical preparations with antiviral activity have also been tested by inhibiting the spermidine synthesis, which, by conjugation with el5A, plays a certain role in cell translation [*Firpo M et al., 2020*]. Thus, the authors used diethylnorspermidine molecules, which enhances the activity of spermidine-spermine acetyltransferase and the cleavage of this polyamine, as well as other compounds, deferiprone and ciclopirox, which inhibit deoxyhypusine hydroxylase, since they target different stages of the polyamine pathway. At the same time, the most effective in the treatment of some viral infections, including those caused by certain coronaviruses pathogenic for humans (but not SARS-CoV-2), according to these authors, turned out to be the use of a DFMO-irreversible ODC inhibitor, which blocks the chain of the cascade reactions at the earliest stages of polyamine synthesis, i.e. preventing the synthesis of putrescine from ornithine.

Firpo M. and co-authors (2020) believe that DFMO introduction may be a promising step in suppressing viral replication. So, the use of DFMO turned out to be relatively effective in the course of the infectious process caused by some representatives of the coronavirus family.

Despite numerous very promising therapeutic and preventive studies by a number of advanced researchers, in which the tactics of using DFMO in the treatment of coronavirus diseases, including COVID-19, are decisively presented. DFMO, un-

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fortunately, continues to be outside the generally accepted (not always effective) COVID-19 treatment regimen. In this publication, the authors, highly appreciating the contribution that the above-named studies have made and continue to make to modern virology and infectious epidemiology, express their full solidarity in the "fair agitation" of using DFMO in COVID-19. It is noteworthy that for some diseases (in particular trypanosomiasis), DFMO is a first-line drug and is included in the list of essential drugs by the World Health Organization [*Firpo M, Mounce B, 2020*].

One of the ways to ensure the optimal content of polyamines in the mammalian body is their intake with food.

Considering the circumstance that there is a polyamine deficiency in the cells of various organs in SARS-CoV-2 infected patients, due to the fact that coronaviruses begin to "utilize" intracellular polyamines for activation in the macroorganism, in our opinion, the studies aimed at significantly limiting the polyamine-rich food from the dietary of COVID-19 patients seem very relevant. We are talking about a "polyamine-free and/or low polyamine" diet. This approach with specific recommendations will serve as the subject of our separate report, which we plan to publish in the "New Armenian Medical Journal" in 2021.

In conclusion, we consider it necessary to once again (due to the urgency of the problem) dwell on the following scientific and organizational measures, which will undoubtedly turn out to be effective in the complex treatment of COVID-19.

Firstly, it is highly advisable to create a specialized diagnostic laboratory on the basis of specialized infectious disease clinics in order to determine aliphatic polyamines – putrescine, spermidine and spermine, as well as agmatine and cadaverine, in plasma, erythrocytes and urine. Such studies are also necessary because the biological role of specific aliphatic polyamines in mammals and in the process of persistence of RNA-positive species in a microorganism is far from unambiguous.

Secondly, we consider it expedient to include DFMO or its commercial analogs in the general treatment regimen for COVID-19, especially since these compounds have long been used in the treatment of a number of neurological and oncological diseases as licensed pharmacological agents. It seems quite sufficient if, by using DFMO in patients with COVID-19, mechanisms can be activated that block the very initial stages of contact of the coronavirus with target cells, i.e. attachment (adhesion) of the virus to the surface of cell membranes of virus-sensitive cells.

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Armen A. Muradyan

Address for correspondence:

Yerevan State Medical University
2 Koryun Street, Yerevan 0025,
Republic of Armenia

Phones:

(+37410) 582532 YSMU
(+37410) 580840 Editor-in-Chief
Fax: (+37410) 582532
E-mail: namj.ysmu@gmail.com, ysmi@mail.ru
URL: http//www.ysmu.am

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Armenia, 0002, Yerevan,
Saryan St., 4 Building, Area 2
Phone: (+374 10) 52 02 17,
E-mail: collageltd@gmail.com

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