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Review Article

Pharmacotherapeutic Treatment Strategies COVID-19: Lessons Learned and Perspectives

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Abstract

The pandemic emergency has created an urgent need to find suitable drugs to treat coronavirus disease 2019 (COVID-19). Numerous drug trials have been conducted; however, effective and affordable treatments have not been found. The study aimed to find ways out of the current situation based on a better understanding of events, based on an analysis of the causes of the difficulties encountered on this issue. The study analyzed articles based on the results of COVID-19 treatment identified in PubMed, Clinical key, ScienceDirect, World Health Organization (WHO), Food and Drug Administration (FDA), and Google Scholar's online libraries. This review summarizes and critically analyzes the information accumulated over the pandemic on the efficacy of drugs for the treatment of COVID-19 and the reasons for the inconsistency in the results of clinical trials on repurposed drugs, and the role of mutations in new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants, in reducing the effectiveness of vaccination and treatment, and determining the possibility of overcoming them in the future. Recent achievements in finding effective ways to combat viral pandemics are shown. According to the results of clinical trials, only remdesivir and sotrovimab have been recommended for the treatment of COVID-19. The prospects in the fight against COVID-19 are the creation of new antiviral drugs, such as cyanorone-20 and antisense oligonucleotides (ASOs), and a proactive strategy for the development of drugs against viral pathogens, which are based on cocktails of panvirus drugs for oral and inhalation administration.

Introduction

The outbreak of a new infection that occurred in Wuhan, China, in December 2019 became officially known as coronavirus disease 2019 (COVID-19). Its potential for widespread and severe disease led to the declaration of a pandemic by the World Health Organization (WHO). The lack of experience to fight it, scientific information and treatment tools, the unusual behavior of the virus and the uncertainty of outcomes in the fight against a new infection created a public health emergency around the world, which generated panic in society about the impending danger.[1] This was the basis for an unprecedented appeal to the world scientific community for a comprehensive study of this problem, based on which almost all the scientific journals of the world opened their pages for the first publications of information on this topic. Despite a sharp increase in relevant information (since the beginning of 2020, the number of publications on the COVID-19 problem has grown <1,000 times), to date there are many more questions than answers.

The scale and duration of the pandemic stimulated a flurry of clinical trials that assessed many different drugs aimed at aspects of the virus life cycle and at maintaining the organism's vitality. Currently, determining the efficacy of potential pharmacological agents for the treatment of COVID-19 is an urgent task. However, readily available, and effective treatments are lacking, and there is a high mortality rate globally.[2,3] A comprehensive analysis of the reasons for the difficulties encountered and the recent divergent opinions of scientists on this problem mean that a deep understanding of the situation is required, and it is popular to find ways out of this situation.

Keywords: COVID-19; SARS-CoV-2; Drug repurposing; Antiviral drugs; Clinical trials.

Abbreviations: ASO, antisense oligonucleotide; 3CLpro, 3C-like protease; COVID-19, coronavirus disease 2019; CYP450, cytochrome P450; FDA, Food and Drug Administration; EUA, emergency use authorization; mAb, monoclonal antibody; IL, interleukin; JAK, Janus kinases; RCT, randomized clinical trial; RdRp, RNA-dependent RNA polymerase; RNA, ribonucleic acid; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2; WHO, World Health Organization.

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Methods

Searches were conducted using the following databases: PubMed, Clinical key, ScienceDirect, WHO, Food and Drug Administration (FDA), and Google Scholar's online libraries to identify published and prepublished studies that reported COVID-19 treatment outcomes from January 2020 to March 2022. Keywords for the search included: COVID-19, SARS-CoV-2, clinical trial, therapy, antivirals, vaccines, and antibodies. Publication types and language were not limited, except for unpublished studies. The following studies were excluded: conference abstracts, case reports, letters, editorials, or comments. The articles of overview, meta-analysis and original nature were used in the review.

Structure and life cycle of severe acute respiratory syndrome coronavirus 2

The cause of the pandemic is a virus officially called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the genome of which encodes many proteins necessary for its transcription and replication (*e.g.*, membrane (M), spike (S), shell (E), nucleocapsid (N), and other proteins). Details of these components are presented in several overview articles.[3,4]

Upon entering the body, the virus enters the cell by priming the S protein with a transmembrane protease (TMPRSS2) of the cell and reacting with the angiotensin-converting enzyme (ACE2) receptor. A key role in this process is played by the spike glycoprotein, which consists of two subunits S1 and S2, the first of which is responsible for binding to the host receptor, and the second plays a role in the fusion of the viral and cell membranes. Upon completion of the fusion process, a viral genome enters the cell, the RNA of which serves as a matrix for translation into structural and non-structural proteins, such as papain-like protease (PLpro), 3C-like protease (3CLpro), and RNA-dependent RNA polymerase (RdRp).[5]

Repurposing used drugs as a method of combating COVID-19

All of these interactions between SARS-CoV-2 and cellular structures have been used as targets for drugs and vaccines.[6,7] Therefore, efforts have focused on testing known drugs, because the development of a new drug is a long, expensive, and risky process. The main benefit can be the availability of available information on the metabolic profile of drugs, dosage requirements, risks, complications, and side effects, and already produced drugs located in warehouses and pharmacies.[8,9]

There are >50,000 well-known and registered drugs and nutraceuticals, and several hundred have been proposed as anti-COVID-19 candidates; however, only a fraction of them have been tested in clinical trials.[10]

Table 1 shows that the bulk of repurposed drugs that were proposed for clinical trials could block viral replication in SARS-CoV-2 by synthesizing incorrect viral RNA or inhibiting 3CLpro and RdRp, and the rest of the drugs could inhibit the virus's entry pathways into the cell.[11–45]

The analysis of a huge amount of data on various aspects of COVID-19 using artificial intelligence was the basis for the development of a new alternative drug detection strategy. The drug repurposing process was carried out with various methods and approaches: computer modeling (an approach based on targets and the orientation of drugs approved by the FDA); phenotypic screening; binding analysis; molecular docking; microsimulation analysis; structure-based machine learning strategies; network approaches; and hybrid methodologies.[46–49]

For computer reprofiling, a three-dimensional protein target structure was created, based on which 7,173 drug molecules were tested in combined databases (DrugBank and KEGG) and 16 candidate drugs were proposed for future studies and an atlas of anti-COVID-19 compounds.[49–52] Similarly, differential gene expression that was associated with the development of pneumonia and cytokine storm syndrome in COVID-19 was analyzed.[53]

All drugs were tested *in vitro* and of these 216 had a pronounced blocking effect on the reproduction of SARS-CoV-2 in cell cultures.[46,54] However, most of these experiments were performed on a non-representative Vero E6 kidney cell line, which had a distant resemblance to lung epithelial cells.[54,55] For example, SARS-CoV-2 penetrates Vero E6 cells by fusion in endosomes, and into lung cells by fusion with the cell surface after activation of the virus spike by cell protease TMPRSS2.[56] In addition, for an antiviral agent to be effective in the treatment of COVID-19, it must reach sufficient concentrations to suppress viral replication in any area of the body. In addition, there is very little information about these processes, and a limited number of publications have studied the pharmacokinetic and pharmacodynamic parameters of such drugs.[14,57] Therefore, low concentrations of unbound lopinavir in lung tissues limited its efficacy in patients with COVID-19.[58] Similar results were shown for ribavirin and amantadine.[59]

Therefore, the insufficient effectiveness and safety of the drugs that were identified in subsequent clinical trials caused their failure, especially demonstrated by the example of the widely advertised drugs, such as hydroxychloroquine and ivermectin.[60]

Efficacy and challenges in clinical trials of drugs against COVID-19

The study of the efficacy and safety of various drugs for the treatment of COVID-19 created the need for well-planned randomized clinical trials (RCTs). Many national and international clinical trials have been conducted on drugs but most have shown conflicting results or identified different limitations.[61,62]

Therefore, why has the rush to find cures for COVID-19 led to problems with interpretation and deciding on the results of some clinical trials? It is possible that because of the emergency, many drugs were evaluated in clinical trials that were not randomized, controlled, or blinded with a clear consensus on endpoints, primary, and secondary outcomes, which did not rule out bias and limited information received.[63] Therefore, the true efficacy, toxicity, or side effects of these drugs were detected during their subsequent use. Only 29% of the available data on COVID-19 pharmacotherapy were based on moderate to high confidence in the evidence and were therefore reflected in clinical practice. The rest of the information had low or very low reliability of evidence, and therefore, further studies were required to obtain firm conclusions.[61,62,64]

An example of the possibility of effective and timely clinical drug trials, even in emergency settings, is the large RCTs that were conducted by the UK NHS (RECOVERY) and WHO (SOLIDARITY). By collecting data from 12,000 patients from 176 centers in 3 months, the RECOVERY study demonstrated a 90% chance of a reduction in mortality. SOLIDARITY, due to its international scale, made it possible to draw conclusions for patients with different genetic backgrounds and allowed an insight into the mechanisms of drug action to be gained.[61,65] Therefore, final data were

Table 1. Antiviral Drugs Used for COVID-19

Number	Drugs	Related disease	Mechanism of action	Recommendation	Administration
1	Remdesivir[14,18–22]	Ebola virus, Marburg virus infections	RdRp inhibition	In mild-to-moderate, severe, or critical COVID-19	Injection
2	Favipiravir[33,34]	Influenza	RdRp inhibition	In mild-to-moderate COVID-19	Orally
3	Umifenovir[26]	Influenza, HCV, HBV	Viral endocytosis inhibition	In mild-to-moderate COVID-19	Orally
4	Sofosbuvir/daclatasvir[17]	HCV	Nucleoside analog, polymerase inhibition	Severe COVID-19	Orally
5	Molnupiravi[17,23–25,40]	Influenza	Virus RNA mutagenesis	In mild-to-moderate COVID-19	Per orally
6	Lopinavir/ritonavir[41,42]	HIV/AIDS	3CLpro inhibition	In mild-to-moderate, severe, or critical COVID-19	Orally
7	Interferon -β[15]	Multiple sclerosis, HBV, HCV	Balances the expression of pro- and anti-inflammatory agents	Severe or critical COVID-19	Injection
8	Amantadine[17]	Parkinson's disease	It inhibits viral entry into host cells and the release of RNA from the capsid	In mild-to-moderate COVID-19	Orally
9	Paxlovid (PF-07321332/ ritonavir)[40,43]	New	3CLpro inhibition	In mild-to-moderate COVID-19	Orally
10	Camostat mesylate[11]	Pancreatitis	TMPRSS2 inhibition	Severe COVID-19	Orally
11	Nirmatrelvir/ ritonavir[39,45]	New	It inhibits protease Mpro or 3CLpro	In mild-to-moderate COVID-19	Orally
12	Ivermectin[35–38]	Antiparasitic agent	It binds and destabilizes the IMPα/β1 complex inhibiting SARS-CoV-2 infection	In mild-to-moderate COVID-19	Orally
13	Niclosamid[17]	Antiparasitic agent	Prevention of viral entry and replication by altering endosomal pH and inhibition of autophagy	In moderate to severe COVID-19	Orally
14	Rivaroxaba[11]	Anticoagulant	TMPRSS2 inhibition	In moderate to severe COVID-19	Orally
15	Bamlanivimab/ etesevimab[27,29–31]	New	It binds (S) protein of SARS-CoV-2	In mild-to-moderate COVID-19	Injection
16	Tixagevimab/ cilgavimab[27,28]	New	It binds distinct epitopes of the viral spike protein receptor-binding domain	In mild-to-moderate COVID-19	Injection
17	Casirivimab/ imdevimab[32]	New	It binds distinct epitopes of the viral spike protein RBD SARS-CoV-2	In mild-to-moderate COVID-19	Injection
18	Amubarvimab/ romlusevimab[44]	New	It binds distinct epitopes of the viral spike protein RBD SARS-CoV-2	In mild-to-moderate COVID-19	Injection
19	Sotrovimab[16]	New	It binds (S) protein of SARS-CoV-2	In mild-to-moderate COVID-19	Injection
20	Regdanvimab[16,44]	New	It binds distinct epitopes of the viral spike protein receptor-binding domain	In mild-to-moderate COVID-19	Injection
21	Adintrevimab[16]	New	It binds distinct epitopes of the viral spike protein receptor-binding domain	In mild-to-moderate or prevention of COVID-19	Injection

HBV, viral hepatitis B; HCV, viral hepatitis C; RBD, receptor binding domain.

Table 2. Immunomodulatory drugs used for COVID-19

Number	Drugs	Related disease	Mechanism of action	Recommendation	Administration
1	Mavrilimumab[53,73]	Rheumatoid arthritis	GM-CSF receptor inhibition	Severe COVID-19	Injection
2	Infliximab[16,73]	Autoimmune arthritis and Crohn's disease	TNF-α inhibition	Severe or critical COVID-19	Injection
3	Adalimumab[28,70]	Rheumatoid arthritis	TNF-α inhibition	Severe COVID-19	Injection
4	Tocilizumab[57,71]	Rheumatoid arthritis, Castleman's disease, giant cell arteritis	IL-6 receptor inhibition	Severe COVID-19, cytokine storm	Injection
5	Sarilumab[16,27]	Rheumatoid arthritis	IL-6 receptor inhibition	In moderate to severe COVID-19	Injection
6	Levilimab[16]	Rheumatoid arthritis	IL-6 receptor inhibition	Cytokine storm	Injection
7	Sirukumab[28,70]	Rheumatoid arthritis, Castleman's disease	IL-6 receptor inhibition	Cytokine storm	Injection
8	Siltuximab[70]	Rheumatoid arthritis	IL-6 inhibition	Cytokine storm	Injection
9	Lenzilumab[28,50]	Chronic myelomono cytic leukemia	GM-CSF receptor inhibition	Severe COVID-19	Injection
10	Risankizumab[73]	Psoriasis	IL-12/IL-23 inhibition	Cytokine storm	Injection
11	Ixekizumab[15]	Autoimmune diseases	IL-17 inhibition	Cytokine storm	Injection
12	Canakinumab[15,27]	Juvenile idiopathic arthritis and active Still's disease	IL1 β inhibition	Cytokine storm	Injection
13	Emapalumab[28]	Hemophagocytic lymphohistiocytosis	Interferon-γ inhibition	Cytokine storm	Injection
14	Anakinra[53]	Rheumatoid arthritis	IL-1 receptor inhibition	Cytokine storm	Injection
15	Baricitinib[53]	Rheumatoid arthritis	JAK1 H JAK2 inhibition	Severe COVID-19, cytokine storm	Orally
16	Imatinib[53]	Cancers	JAK inhibition	Severe COVID-19	Orally
17	Tofacitinib[53,72]	Rheumatoid arthritis	JAK1, JAK2, JAK3 inhibition	Severe COVID-19	Orally
18	Ruxolitinib[47,69]	Myelofibrosis, polycythaemia vera, rheumatoid arthritis	JAK inhibition	In moderate to severe COVID-19	Orally
19	Colchicine[53,74]	Gout, pericarditis, and coronary artery disease	Inflammasome formation and interleukins release inhibition	severe COVID-19, cytokine storm	Injection Orally
20	Dexamethason[50]	Skin diseases, severe allergies, asthma *etc*.	Proinflammatory cytokine production inhibition	Severe COVID-19	Injection Orally
21	Budesonide[17]	Asthma	TMPRSS2 and ACE2 expression decrease	Severe COVID-19	Inhalation

GM-CSF, granulocyte–macrophage colony-stimulating factor; TNF-α, tumor necrosis factor.

obtained on the effectiveness or the inefficiency of several drugs.

The consideration of COVID-19 clinical stages and severity is extremely important when prescribing certain drugs, which depends on the mechanism of their action and the correct assessment of treatment effectiveness (*e.g.*, to determine the endpoints, primary, and secondary outcomes of clinical trials).

According to clinical data, COVID-19 is divided into three sequential stages. The first stage is defined as early or viral when SARS-CoV-2 replicates intensively in the body with the manifestation of positive PCR tests and acute inflammatory symptoms. During this period, patients have mild-to-moderate severity of states and, depending on the ratio of innate immune response and depletion of target cells available for infection, with appropriate care under outpatient conditions, usually recover.[66–68] The most preferred treatment here is the antiviral drug administration that has been repurposed for other viral infections (Table 1).

In 5%–10% of cases, a transition to the second stage was observed with the development of a severe course of the disease with respiratory and multi-organ insufficiency (up to critical with fatal outcome), which required hospitalization. This stage, defined as late or hyperinflammatory (cytokine storm), was characterized by the explosive release of cytokines, of which IL-6 appeared to be predominant and was correlated with the severity of the condition. Since IL-6 hyperproduction was detected in many diseases, including chronic inflammatory diseases and cancer, the drugs used to treat them showed their effectiveness against COVID-19[15-17,27,28,47,50,53,57,68–74] (Table 2). Survivors in stage three might develop some organ problems, the treatment of which is not

a subject of this review.

As described previously, this could explain why most antiviral drugs did not show their effectiveness in mortality, steroids and some anti-cytokine drugs could worsen the patient's condition in the early stages of COVID-19, and a universal drug was never detected.

Clinical trials of drugs repurposed for COVID-19

At the beginning of the pandemic, there were no specific anti-SARS-CoV-2 agents, and clinical outcomes were associated with the use of maintenance therapy. The first antiviral drug to receive permission for emergency use (EUA) (in May 2020) was remdesivir, a prodrug in the form of adenosine monophosphate, which, according to some RCTs, led to accelerated clinical improvement in hospitalized patients and reduced the incidence of hospitalizations during the early stage of the disease by 80%.[18] However, SOLIDARITY and multicenter DisCoVeRy studies failed to identify reductions in remdesivir mortality.[19,20,65] Because of these conflicting results, >RCTs have been or continue to be conducted to date to comprehensively assess the efficacy of remdesivir, alone and in combination with other drugs.[21,22]

A similar outcome was determined for molnupiravir, which demonstrated a strong antiviral effect in *in vitro* studies.[23] Under its effect, on day 5 of outpatient treatment, complete disappearance of the virus from the body and an approximately 50% decrease in the frequency of hospitalizations were revealed.[24] However, if hospitalized patients with non-severe COVID-19 there had a decrease in the rate of disease progression and mortality, then in the progressive and severe course of disease no significant results were achieved.[23,25]

Hydroxychloroquine and chloroquine, which are used for the treatment of rheumatoid arthritis and malaria, were among the first drugs used in the fight against COVID-19.[75] Although they were quite effective from *in vitro* experiments, large RCTs, such as SOLIDARITY and RECOVERY showed no significant benefit for them in severe conditions.[26,60,65] Therefore, they were not recommended for use in monotherapy; however, they were continued to be tested in combination with other drugs. However, their use as a monotherapy and in combination with azithromycin could increase the risk of extending the QT interval, threatening cardiac arrest in some people, especially those suffering from heart disease.[76] Based on analysis of many RCTs, WHO does not currently recommend the use of hydroxychloroquine or chloroquine, azithromycin, and lopinavir or ritonavir for the treatment of COVID-19.[65]

Clinical trials of monoclonal antibodies against SARS-CoV-2

Monoclonal antibodies (mAb) were used as antiviral drugs, most of which (Table 1) inhibit the entry of SARS-CoV-2 into cells by their attachment to various epitopes of its (S) protein.[27,70,73] The results of clinical trials demonstrated that the best efficacy of such antibodies was manifested in the treatment of patients in the early phase of COVID-19 and with mild-to-moderate severity of the condition.

However, the ability of SARS-CoV-2 to rapidly mutate, especially in the region of the (S) protein, caused the loss of antibody activity that had a target in the mutated region.[28,70] An example of this is bamlanivimab, which was the first mAb to receive FDA approval in November 2020 based on successful test results under RCT BLAZE-1, ACTIV-2, and ACTIV-3. The emergence of new variants of the bamlanivimab-resistant SARS-CoV-2 virus forced the FDA in April 2021 to revoke its permission for the emergency use of bamlanivimab, when prescribed as monotherapy.[29] However, the detected sensitivity of the Delta variant of SARS-CoV-2 to the combination of bamlanivimab and etesevimab allowed the FDA to reconsider its opinion and issue a permit for their emergency use as post-exposure prevention for COVID-19 in individuals at high risk of disease progression.[30,31]

Antibody combinations prevent the mutated virus from escaping neutralization; therefore, biotechnology companies have begun to develop cocktails of mAb pairs that target various structural epitopes of the (S) protein. This proved successful for antibody cocktails, such as casirivimab + imdevimab (Regeneron Pharmaceuticals) and tixagevimab + cilgavimab (Astra Zeneca). Although the efficacy of the first cocktail is still being tested as part of the RECOVERY study, to date, permission for its emergency use for the treatment of COVID-19 has been granted in 15 countries around the world. For the second cocktail, decisions will be made by USA and EU regulators on conditional permission to sell.[32,70] To date, only one mAb (sotrovimab) did not lose its activity to mutated SARS-CoV-2. Therefore, sotrovimab, which showed the possibility of reducing the risk of patient deterioration by 85% in 24 h, received approval for use in COVID-19 in the USA, UK, and EU from December 2021.[27]

Drug combination considering their pharmacokinetic profile to improve the treatment effectiveness of COVID-19

Analysis of the results of anti-COVID-19 drug trials allowed White *et al.*[77] to propose the development of drug combinations to increase efficacy, reduce doses, and side effects, which has been achieved for human immunodeficiency viruses and hepatitis C. They identified 34 reports on 77 combinations of unique pairs of low molecular weight drugs against SARS-CoV-2. The largest number of them (62 pairs) included remdesivir or molnupiravir, which are inhibitors of RdRp with different biochemical mechanisms.

When using paired synergy for potential therapeutic action, the pharmacokinetic profiles of drug components might be crucial. Since *in vitro* evaluation can give 5–10 times an overestimated picture of antiviral effects in humans, to establish the association between the plasma concentration of drugs with antiviral effect, it is important to carry out serial measurements of viral load combined with mathematical modeling.[59,78]

An example is the clinical trials of favipiravir (nine RCTs mainly in China and some Asian countries), which showed accelerated virus elimination and clinical improvement in patients with mild-to-moderate COVID-19.[33] However, in severe cases of patients that received the recommended dose of favipiravir, a low level of the drug in the blood (1 μg/mL) was detected, which did not have the desired therapeutic effect.[34] This might be due to a change in the activity of enzymes (in particular, CYP450-3A) due to the serious condition of the patients or the direct influence of favipiravir on them.[79] That is why small studies failed to show significant differences in the co-administration of favipiravir with other drugs (*e.g.*, hydroxychloroquine, lopinovir or ritonavir, and baloxavir), the inefficiency of which was proved later.[33]

The possibility of enhancing the effect of co-administrated drug under the influence of CYP450 inhibitors was characteristic of remdesivir. It is a prodrug that metabolizes rapidly into an active analog of GS-441524. The enzymes that activate it are expressed more in liver and kidney cells than in the lungs, the impaired func-

tions of these organs can significantly reduce the active substance concentration of remdesivir.[14,79] A similar situation occurred with ivermectin, whose pharmacokinetics are characterized by rapid metabolism in the liver (by the CYP450 enzyme system).[35,79] Although ivermectin in cell cultures could inhibit 5,000-fold SARS-CoV-2 replication in 48 h of incubation, clinical studies have produced conflicting results regarding mortality, disease progression, and duration of hospitalization, especially when the patients have a serious condition.[36–38] Therefore, it was not recommended for routine use with COVID-19.

The need to maintain an appropriate concentration of drugs in the body was a reason to combine some antivirals with ritonavir in a single dose form. In addition, ritonavir which is inhibitory against viral proteases and CYP450-mediated metabolism contributed to increased concentrations of lopinavir and nirmatrelvir.[39,40] However, individual differences in CYP450 enzyme activity and this situation could cause ambiguity in the results of clinical trials. Faster recovery and lower mortality relative to standard treatments were shown in one open RCT that was conducted in China at the start of the COVID-19 pandemic, subsequent RCTs, such as SOLIDARITY and RECOVERY, did not reveal any significant efficacy of the drugs among patients hospitalized with COVID-19.[41,42] The individual differences in efficacy could not yet been established for other such drugs, since they have not yet reached major clinical trials. For example, paxlovid, which is a combination of nirmatrelvir with ritonavir, showed an 89% decrease in hospitalization and mortality rates during an intermediate phase III analysis of clinical trials, based on which it was submitted to the FDA for EUA.[40,43]

Use of vaccines for COVID-19

It is widely recognized that vaccine prevention is the most effective method of preventing and eliminating any infection. According to WHO, almost 7.7 billion doses of vaccines were used at the beginning of 2022, and approximately 53.2% of the world's population has received at least the first dose of the vaccine.[80,81]

Immediately after the pandemic began, several laboratories began to create vaccines against SARS-CoV-2 and >200 candidate vaccines were involved in this process. According to WHO, 69 vaccines are in clinical development worldwide, and 181 are in different stages of preclinical development.[82]

To date, there is no unified world policy or consensus on the choice of vaccines. In addition to efficiency and safety parameters, many factors play a role in the implementation of the latter, which include costs, accessibility, warehouses, national competition, and commercial considerations.[83] Although the international debate on the risk or benefit assessment of vaccines has been driven by some commercial considerations, in general, most approved SARS-CoV-2 vaccines have proved to be somewhat effective. However, data on the evaluation of the effectiveness of vaccines against COVID-19 are limited and contradictory, and numerous studies have revealed a weakening of immunity acquired because of vaccination.[84–86] However, there is no available information on the long-term toxic or adverse effects of various vaccines that are normally required in drug development, which is due to extraordinary and rapid regulatory approvals.[86,87]

In general, the use of most vaccines has been concentrated in a small number of highly developed countries, and the rest of the world remains susceptible to this infection.[83,88] In addition, during the pandemic, it was not possible to completely prevent infection of the population, since emerging mutations in new versions of the SARS-CoV-2 allowed them to avoid an immune response. Therefore, this is currently relevant due to the extremely rapid spread of the new viral variant Omicron.[89]

The problem of combating Omicron, a new version of the mutation SARS-CoV-2

During the pandemic, WHO named five variants of SARS-CoV-2 (Alpha, Beta, Gamma, Delta, and Omicron) that have already spread throughout the world.[1,2] In addition, >80 mutations have been identified in various areas of the SARS-CoV-2 virion, of which the (S) protein is the most often modified.[89,90] In addition, the existing types of vaccines are mainly aimed at this particular protein, and the developed types of vaccines could be aimed at other molecular targets.[3,84]

Calculating the rate of mutation formation in SARS-CoV-2 showed that the virus accumulated approximately 2 single-nucleotide mutations per month in its genome. Moreover, the largest number of mutations (>50) was detected in the Omicron variant, of which 32 mutations were localized in the spike protein. This appeared to have increased its ability to evade antibodies and the T cell response.[91–93] Therefore, the existing vaccines were less effective against Omicron.[94,95] Therefore, the effectiveness of the Pfizer-BioNTech vaccine for Omicron decreased to 33%, and for the Delta variant, it was 80%. In addition, the potential of re-infection with the Omicron variant reached 60% for people who had Beta variant SARS-CoV-2 but was only 40% for people who had Delta variant SARS-CoV-2.[96]

Therefore, in this development, the importance of antiviral therapy increased significantly, especially for the protection of people most vulnerable to severe COVID-19.[97] However, with the advent of new variants of the virus, the risk of them forming a resistance to vaccines and antiviral therapy increased.[98,99] Therefore, according to some *in vitro* studies, the sensitivity of Beta and Gamma variants of SARS-CoV-2 was reduced to combinations of monoclonal antibodies, such as bamlanivimab and etesevimab, in contrast to the Alfa, Delta, and Lambda variants.[44,100] Therefore, many of the drugs that showed good efficacy in *in vitro* studies showed conflicting results or had various limitations in clinical use.

Intensive research has begun with the Omicron variant of SARS-CoV-2. Therefore, testing the dose-dependent effects of drugs that had various methods of application and mechanisms of antiviral action (*e.g.*, remdesivir, favipravir, ribavirin, nirmatrelvir, nafamostate, camostat, and aprotinin) revealed the same sensitivity of the Omicron and Delta variants to them. In addition, the first four drugs could inhibit RdRp in various ways, and the last three could block cleavage of the viral (S) protein by cell proteases, in particular, TMPRSS2.[101] Similar results were obtained by Vangeel *et al*.[45] for remdesivir, molnupiravir, and nirmatrelvir. This demonstrated that in the Omicron SARS-CoV-2 variant there were no mutations that caused significant changes in medicinal sensitivity patterns.

However, by the end of 2021, the Omicron SARS-CoV-2 variant revealed a second subvariant of BA.2, which was 1.5 times more transmissible than BA.1. BA.2 spike protein, in addition to all mutations BA.1, has six mutations and three deletions, three of which lie in the receptor-binding domain.[4,102,103] According to Zhou *et al*.,[99] monoclonal antibodies authorized by FDA for EUA, which included Regeneron's REGN10933 and REGN10987 and Eli Lilly's LY-CoV555 and LY-CoV016 were inactive against BA.1, and GlaxoSmithKline's Vir Vir-7831 and the cocktail AstraZeneca Evusheld (AZD8895 + AZD1061), could neutralize it. For the subvariant BA.2, only the last cocktail was neutralizing. This showed that the Omicron variant poses a serious threat to

the effectiveness of current therapies, especially monoclonal antibody therapy. In this situation, Zhou *et al*.[99] suggest the use of molnupiravir and nirmatrelvir, which act on viral targets outside of the highly mutated (S) protein. For vaccination, they recommend the use of vaccines that induce cross-reactive antibodies and T cell responses against unmutated (S) protein epitopes.

Omicron is seven times more contagious than the Delta variant, and the number of reported cases and deaths in Africa; however, according to the African Medical Association, continues to decline, and Omicron infection is not accompanied by a serious deterioration in the condition of patients.[94,104,105] The lower pathogenicity of Omicron might be due to a greater sensitivity than Delta variant SARS-CoV-2 to the interferon response in human cells, since many proteins that inhibit the action of interferon (*e.g.*, S, N, and M) have been mutated in the Omicron variant.[106] The low resistance of this variant of the SARS-CoV-2 to interferon was proved in the studies of Bojkova *et al*.[101] by infection with the Delta, Omicron (BA.1 and BA.2 variants), different types of cell culture, which have a different interferon response (Vero cells have a defective response to interferon as opposed to Caco-2 and Calu-3 cells). This indicated the possibility of beneficial therapeutic and prophylactic effects of interferon-containing or interferon-stimulating drugs when infected with the Omicron variant of SARS-CoV-2, unlike other variants.

For patients with COVID-19, under the influence of interferons (INF) β-1a and INF-α2b administered through a nebulizer, more than a twofold increase in the probability of recovery and a decrease in viral load and mortality levels can be achieved.[107] For INF-β-1b, it was necessary to administer it in very high doses as an aerosol and an injection. According to Chong *et al*.,[108] for the Omicron variant, the interferon-λ administered by inhalation was most effective since this method of administration is most convenient in the early stages of COVID-19 at home. These data showed that the therapeutic efficacy of interferon in COVID-19 depends on its type, route, and time of administration, and indicates the need for larger clinical trials.

Preparation of optimal dosage forms for the treatment of COVID-19

In general, only one antiviral drug (remdesivir) and one monoclonal antibody (sotrovimab) have been approved and recommended for the treatment of COVID-19, and they are more effective in the early stage and non-severe forms of the disease.[8,17] However, these drugs need to be administered parenterally, which makes their use difficult, especially at home. In such cases, oral and inhalation pathways are the best options to rapidly reduce viral load during the post-contact period or at the onset of illness. Therefore, research is being carried out on ways to create tablet forms of antiviral drugs (i.e., GS-441524 which is an analog of remdesivir in tablet form has been prepared for clinical trials).[109]

The use of inhalation to deliver drugs for the direct prevention and treatment of COVID-19 has received limited attention, although it might be more effective and less toxic than systemic drug delivery. Several inhalation drugs for the treatment of COVID-19 are currently being prepared for clinical trials, such as interferon, remdesivir, ciclesonide, heparin, budesonide, nicklosamide, and the small inhalation biologics minibinders and peptide fusion inhibitors.[110,111]

In inhalation, drugs are delivered directly to the primary focus of infection in the airways, and there are significant prospects for use of nanoparticles to carry drug substances on their surface.[112,113]

Program to prepare for new outbreaks of viral pandemics

Recent reports of a reduction in the pathogenicity of coronavirus give hope about the potential of an end to the pandemic after Omicron. However, it is predicted that SARS-CoV-2 will not disappear, since its ability to mutate extremely quickly might be the basis for the emergence of new pandemic waves with pathogenicity that is unknown to us. In addition, the likelihood of the appearance of new dangerous types of viruses has not been ruled out. For example, in the literature, there was information about the detection of a novel coronavirus of NeoCoV that could penetrate cells, similar to SARS-CoV-2.[114] The lack of understanding of the NeoCoV nature, which combines high mortality MERS-CoV, and the high rate of current SARS-CoV-2 spread poses a potential threat to biosafety for humanity.

The world was not prepared for the current pandemic and remains vulnerable to future pandemics. If we do not learn from the events of the last 2 years, the consequences could be devastating. According to Brüssow,[61] the pandemic has created several problems for some groups in society (*e.g.*, industry, governments, clinicians, and researchers) that require quick solutions. In addition to the imperfect designs, a lack of coordination and the capacity of clinical trials of drugs, which included extremely low funding for the development of antiviral drugs, compared with investments in the creation of vaccines, and the dual responsibility of the pharmaceutical industry to its shareholders and the public (i.e., the consumers of their products), and the need to develop antiviral drugs with pancoronaviral inhibitory activity.

Therefore White *et al*.[77] proposed a proactive drug development strategy against dangerous viral pathogens. It is necessary to develop plans for two scenarios in the long or short-term, which are based on the possibility of a serious viral outbreak: (1) after approximately 5–10 years; or (2) between ≤1 and 2 years. In addition, both plans should focus on drug combinations; however, in scenario 1 on the development of new chemical compounds, in particular direct-acting antiviral drugs, and in scenario 2 on existing repurposed antiviral drugs.

The drug development program for both scenarios will need to be based on the following five key principles:

1. Providing the benefit of oral and inhalation drugs, which can be taken at home as post-exposure prophylaxis or at the onset of disease, to rapidly reduce viral load and prevent subsequent excessive immune activation.
2. Searching for drug combinations to reduce the possibility of drug-resistant mutants, reduce the necessary doses and mitigate side effects, based on the detection of multiplicative or synergistic actions of drugs.
3. Creating a priority for drugs that are approved or undergoing extended clinical trials to enable a faster regulatory review process. For Plan A, it is possible to additionally include drugs that are currently in preclinical development.
4. Giving preference to drugs whose effective concentrations in the corresponding human tissues will be significantly lower than their toxic concentrations and will remain in the range of achievable levels throughout the dosing interval.
5. The use of mathematical modeling at critical stages of the transition to animal testing and clinical trial design.

The results should be cocktails of panvirus drugs for oral or inhalation administration. To test these drugs in pandemic conditions, a preplanned clinical trial could be immediately conducted. The author proposes to name this approach VORTEC (preparedness for viral outbreaks through effective combinations). Such drug cocktails for home use in combination with other non-phar-

maceutical interventions should significantly reduce the burden on health systems and prevent the spread of the virus.

Prospects in the development of drugs against SARS-CoV-2

Based on global experience in the search for anti-SARS-CoV-2 agents, the blockade of viral RdRp is one of the most promising and effective approaches for the development of potent anti-COVID-19 agents. This group includes the best drugs favipiravir and remdesivir.[6,8]

However, with the help of computational means and *in vitro* studies, the repurposing of existing drugs against COVID-19 is carried out and new ones are being created. Therefore, Rabie[115] reported the development of a new nucleoside or nucleotide analog (cyanorone-20), which is 209 and 45 times more effective than favipiravir and remdesivir, respectively. Such a potent antiviral drug, if it completed preclinical and clinical trials, would find widespread use in the control of COVID-19, especially when used in oral or inhalation forms.

To solve the mutating SARS-CoV-2 problem, Zou *et al*.[116] performed structural and functional analysis on natural antibodies that were isolated from the blood of patients recovering from COVID-19. By scanning them using a library of receptor binding domains of yeast spike protein, they revealed rare, ultrapotent, mutation-resistant antibodies against SARS-CoV-2. The target of such antibodies is the epitope K378 of SARS-CoV-2 (S) protein, which was not mutated in any of the virus variants, since this led to a complete loss of pathogenicity. This opens the prospect of creating antiviral drugs and vaccines that do not lose their effectiveness in any SARS-CoV-2 mutations.

ASOs, which are short synthetic DNA or RNA molecules, have great promise in the fight against COVID-19.[117] They are designed to target coding and non-coding RNA to adjust the level of their expression. If used as antiviral agents, they act as structural blockers, which by masking a certain RNA sequence make it inaccessible to spliceosome members or transcription factors.[118] In addition, there is almost no consumption of ASOs, which allows them to be used at nanomolar concentrations, reducing the possibility of side effects and other negative phenomena associated with the action of traditional drugs.[118,119] High target specificity and dual mechanism of action, the possibility of use for viruses with a high frequency of mutations, minimal toxicity, and relatively low cost of production due to simplicity of design and speed of development suggest that ASOs have significant potential as drugs against COVID-19.[117,120]

Currently, several firms have patented some ASO against the SARS-CoV-2 virus that has various targets and mechanisms of action, such as destroying the pseudoknot in the place of frameshift of virus RNA (Ionis Pharmaceuticals), inhibiting replication of a virus by the impact on 3′-the end of a negative chain of virus RNA (AVI BioPharma, Inc), the blocking ORF1 AUG (217-245 items of N) the site of a virus genome (Stein David).[117] The antiviral capability of ASOs has long been known; however, none of these molecules have been approved by FDA.

Conclusions

Since the beginning of the COVID-19 pandemic, humanity has been faced with the problem of finding treatments and drugs for a completely new disease for which there was no evidence-based therapy. Initial efforts focused on a drug repurposing strategy, which was a quick way to use new prescribing of existing drugs. Many clinical trials were conducted, most of which were poorly coordinated and insufficiently powerful; therefore, they ended with conflicting conclusions. The incorrect choice of trial endpoints and lack of knowledge of drug pharmacokinetics and pharmacodynamics parameters in several small clinical trials contributed to decisions predominantly based on probability rather than clinical evidence, which later proved ineffective.

The most informative and defining were large, randomized trials of treatments, and based on the results remdesivir and sotrovimab have been recommended to date. However, mutations appearing in new SARS-CoV-2 variants (especially in Omicron) created an opportunity for them to avoid an immune response, which reduced the effectiveness of vaccinations and treatments; therefore, combinations of drugs and antibodies with different targets and mechanisms of action were created and tested. In addition, RdRp and unmutating K378 epitope of SARS-CoV-2 (S) protein is an excellent target for the development of drugs and vaccines against this virus in the future. A powerful inhibitor of RdRp (cyanorone-20) and a new class of drugs (ASO) have great potential as drugs against COVID-19. A proactive drug development strategy based on pan-virus cocktails for oral or inhalation administration has been proposed. In the future, these developments could be a powerful tool when creating new therapeutic strategies to combat COVID-19 and possible future pandemics.

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Conflict of interest

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Author contributions

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