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Case Report

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The Role of Monoclonal Antibodies in the Prevention of COVID-19 Infection and their Role in the Treatment of Patients with Complicated forms of the Infectious Disease (Literature Review)

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ABSTRACT

Summary: The place of monoclonal body drugs in the prevention of covid-19 virus infection and their role in the treatment of patients with complicated forms of the infectious disease"

The Relevance of the Problem: The global spread of coronavirus disease in many regions of the world has initiated the development and improvement of methods of immunological prevention and treatment of this pathology, contributed to the development of new technologies for the production of large amounts of monoclonal antibodies neutralizing the severe acute respiratory syndrome coronavirus (SARS-CoV-2) and the creation of a number of effective antiviral vaccines. Evaluation of their effectiveness in the prevention and treatment of this infectious disease has become the goal of a number of randomized international studies.

Purpose and Objectives: To determine the usefulness of monoclonal antibodies as a new class of therapeutic agents for the treatment of COVID-19 and predicted types of coronavirus infections.

The Content of the Work: The study of the immunological structure of the covid-19 virus and data from the compiled universal libraries of MATS obtained from healthy human donors made it possible in a short time to identify the molecular structures of the binding domain of the spike (S) protein receptor and use them to obtain antibodies that bind specifically to the angiotensin converting enzyme 2 cellular receptor and block the interaction of the virus with these protein structures in various cells and tissues of experimental animals. The effectiveness of these MATS and antibody cocktail has been confirmed in cellular and organ models of animals infected with SARS-CoV-2, both as a preventive and post-infectious treatment, and evidence of their effectiveness and safety has been obtained in a number of randomized clinical trials.

Keywords: Covid-19, Monoclonal Antibodies, Disease Prevention, Treatment Methods.

Relevance of the Problem

The consequences of the coronavirus disease (COVID-19) pandemic have had a severe impact on public health and the state of healthcare systems worldwide, prompting significant changes in strategies, approaches to treatment, and prevention of viral diseases. As of the end of March 2022, when a significant decline in the incidence rate was observed, according to statistics from the World Health Organization, 500,269,744 cases of infection and 6,192,488 deaths from COVID-19 had already been registered worldwide [1].

The global spread of the disease in many regions of the world has prompted the development and refinement of immunological prevention and treatment methods for this pathology and the creation of a number of effective antiviral vaccines [2, 3]. The increase in morbidity during the pandemic has stimulated research at a number of research centers to develop new treatment methods, including the administration of antibodies with the blood plasma of recovered patients. This research has also

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facilitated the development of new technologies for producing large quantities of monoclonal antibodies that neutralize the severe acute respiratory syndrome coronavirus (SARS-CoV-2). In a short period of time, at the height of the epidemic, six monoclonal antibodies were developed and received emergency use authorization (EUA) from drug regulatory agencies in the United States and South Korea [4-6].

The development of new, effective immune therapies to mitigate the impact of the COVID-19 pandemic has become an urgent global need worldwide. Numerous studies have found that neutralizing antibodies are effective antiviral agents because they can be rapidly deployed to prevent disease progression and can accelerate patient recovery without the need for fully developed host [7,8]

Monoclonal antibody (mAb) drugs have revolutionized the treatment of a number of human diseases, including cancer, autoimmune conditions, and inflammatory conditions, according to a number of scientific publications. Their widespread use in medical pharmacotherapy represents a new stage in the treatment of infectious diseases. Over the past decade, innovative immunological methods have enabled the rapid isolation of antibodies from recovering subjects, humanized animals, or in vitro libraries, demonstrating that mAbs can be effective against emerging, highly virulent pathogens and their mutant forms. Over the past five years since the onset of the COVID-19 epidemic, a very large number of mAbs have been developed to combat coronavirus disease 2019 (COVID-19) [9].

Monoclonal antibody therapy offers significant potential for the prevention and treatment of COVID-19. As early as March 2020, the China Antibody Society was established in the region of the initial outbreak of this viral infection and in the United States to coordinate measures for the immunological protection of the population from the risk of the spread of COVID-19. In collaboration with the Antibody Society, the Society initiated the "COVID-19 Antibody Therapeutics Tracker" program (Tracker) to track antibody-based interventions in preclinical and clinical research developments worldwide (China Antibody Society, Cambridge, MA, USA). The US Antibody Society (Framingham, MA) , the National Cancer Institute, and the National Institutes of Health (Bethesda, MD, USA) actively participated in the work of the Society and the development of new mAbs [10].

A new database, called CoV-AbDab, created in Europe by members of the Oxford Protein Informatics Group and experts from the Department of Statistics at the University of Oxford (UK), contained data on more than 1,400 published or patented antibodies and nanobodies that bind to at least one betacoronavirus, representing the first library of antibodies binding to both SARS-CoV-2 and other betacoronaviruses such as SARS-CoV-1 and MERS-CoV (Raybould MIJ, et al. 2021) [11]. Experts from these organizations and structures found that most protein compounds among the candidate antibodies against SARS-CoV-2 appear to target the viral spike protein (S protein) and many of them are full-length monoclonal antibodies (Yang L, et al. (2020), [12]. The list of antibodies blocking the S protein of the SARS-CoV-2 coronavirus included data from clinical trials, including mAbs LY-CoV555, REGN-COV2, JS016, TY027, CT-P59, BRII-196, BRII-198 and SCTA01. It was assumed that clinical evaluations and trials of neutralizing SARS-CoV-2 antibodies will help determine the usefulness of these antibodies as a new class of therapeutics for the treatment of COVID-19 and predicted types of coronavirus infections [12].

By August 2020, the US Coronavirus Drug Research Database (CoV-RDB; covdb.stanford.edu) contained data on over 2,800 cell culture experiments, penetration assays, and biochemical experiments, as well as over 250 animal model studies and 70 clinical trials from over 400 published articles. More than 80% of this body of scientific information contained data on SARS-CoV-2, SARS-CoV, and MERS-CoV. According to researchers at the Division of Infectious Diseases at Stanford University School of Medicine (Stanford, California, USA), approximately 75% of the experiments used novel compounds, including monoclonal antibodies and receptor binding inhibitors, viral protease inhibitors, host-active inhibitors and polymerase inhibitors, interferon-class agents, fusion inhibitors, and animal or human cell protease inhibitors. Of the more than 970 compounds with established or putative mechanisms of action, over 14% were licensed in the US for other indications, and in 60% of cases these were preclinical drugs or compounds [13,14].

The search for antibodies that block the S protein of the SARS-CoV-2 coronavirus included data from a number of clinical studies characterizing the mAb drugs LY-CoV555, REGN-COV2, JS016, TY027, CT-P59, BRII-196, BRII-198, and SCTA01. Clinical trials of these SARS-CoV-2 neutralizing antibodies were expected to help determine their utility as a new class of therapeutic agents for the treatment of COVID-19 and predicted, including mutating, types of coronavirus infections [12]. During this period, the use of various virus-neutralizing antibodies for the treatment of coronavirus infection was approved by the US Food and Drug Administration (FDA) in 2020–2021 [4–6].

Immunological and Biochemical Foundations and Prerequisites for the Creation of Monoclonal Antibody Preparations and their use for the Prevention and Treatment of Patients with Covid-19

According to studies conducted by specialists in biochemistry, immunology, virology, pharmacology and public health, human monoclonal antibodies (mAbs) that neutralize severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its variants represent a promising opportunity for the prevention of viral damage and infection, as well as the treatment of already developed disease and the elimination of post-COVID organ changes in recovered individuals [8]. Most human monoclonal antibodies (mAbs) that neutralize SARS-CoV-2 recognize the receptor-binding domain of the spike protein (S) and block the interaction of the virus with the cellular receptor angiotensin-converting enzyme 2, angiotensin II type coupled to the G protein (GPCR), (Suryadevara N, et al. 2021), [15]. The spike (S) protein of the CoV-2 virus may be the primary target of neutralizing antibodies (nAbs). These antibodies mostly target either the receptor binding domain (RBD) or the N-terminal domain (NTD) of the spike glycoprotein [11-15].

According to a meta-analysis conducted by British authors from the University of Oxford (Oxford Protein Informatics Group), 1130 out of 1400 antibodies and nanobodies against coronavirus bind to SARS-CoV-2 through these structures [11]. American

immunologists from the Department of Biology and Biological Engineering at the California Institute of Technology (Pasadena, California, USA) Barnes CO, et al. (2020), divide RBD-specific NAbs into 4 main classes (I, II, III and IV), [9,16,17]. Class I and II NAbs (nATs) interact with the angiotensin-converting enzyme 2 (ACE2) binding region or the "receptor-binding motif" (RBM) region of the RBD on the spike glycoprotein [16]. Structural comparisons allowed the researchers to classify the antibodies into the following categories: neutralizing antibodies encoded by the VH3-53 gene segment with short CDRH3 loops that block ACE2 and bind only to the "upper" RBDs, neutralizing antibodies that block ACE2 and bind to both the upstream and downstream RBDs and can bind to adjacent RBDs, neutralizing antibodies that bind outside the ACE2 site and recognize both upstream and downstream RBDs, and previously described antibodies that do not block ACE2 and bind only to downstream RBDs [13,16,17]. The RBM region is responsible for the initial contact with the host ACE2 receptor to initiate viral entry [18]. Class IV antibodies, core region I-dependent NAbs, have broad neutralizing activity against SARS-CoV-2, its variants, and other related coronaviruses [11,13,16,19]. More recently, NAbs targeting novel epitopes on the S2 domain (the stem helix region) of the spike have been identified that have broad neutralizing activity, i.e., neutralize SARS-associated and other human coronaviruses (hCoVs), [20-23]. Researchers from the Department of Immunology and Microbiology at The Scripps Research Institute (California, USA) presented evidence of pre-existing cross-reactive serum antibodies to SARS-CoV-2 in pre-pandemic donors and the presence of pre-existing cross-reactive memory B cells that are activated during SARS-CoV-2 infection. Their data showed that monoclonal antibodies have varying degrees of cross-reactivity with betacoronaviruses, including SARS-CoV-1 and endemic coronaviruses [20-23].

Immunology studies have found that most human monoclonal antibodies (mAbs) that neutralize SARS-CoV-2 recognize the receptor-binding domain of the spike protein (S) and block the interaction of the virus with the cellular receptor angiotensin-converting enzyme 2 [15]. Most human monoclonal antibodies (mAbs) that neutralize SARS-CoV-2 recognize the receptor-binding domain of the spike protein (S) and block the interaction of the virus with the cellular receptor angiotensin-converting enzyme 2. By analyzing a panel of human mAbs that bind to various epitopes on the N-terminal domain (NTD) of the S protein, obtained from SARS-CoV-2 convalescent donors, researchers from the Vanderbilt University Vaccine Center and Medical Center (Nashville, TN, USA) found that a minority of them have neutralizing activity. However, only two mAbs (mAbs COV2-2676 and COV2-2489) inhibited infection of authentic SARS-CoV-2 viruses and recombinant VSV/SARS-CoV-2 viruses. The authors mapped their binding epitopes using alanine scanning mutagenesis and selection of functional variants that escape neutralization of SARS-CoV-2 S. These studies showed that these antibodies partially neutralize by inhibiting the post-attachment step in the infection cycle of COV2-2676 and COV2-2489, enabling both prophylaxis and therapy, and that Fc effector functions were required for optimal protection. The researchers concluded that viral infection leads to the synthesis of potent monoclonal antibodies specific to the NTD in the body, which use neutralizing and Fc-mediated activity to protect against SARS-CoV-2 infection [15].

Based on the obtained information, several neutralizing monoclonal antibodies (mAbs) to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were developed and found to be effective in preventing COVID-19, and the US Food and Drug Administration (FDA) issued emergency use authorizations for their neutralizing mAbs in outpatients, non-hospitalized patients with mild to moderate COVID-19 [4-6].

Much attention has been paid in the literature to the potential of replacing antiviral therapy with neutralizing monoclonal antibodies, where dosing to ensure adequate neutralizing capacity can be more precise. In an analytical review by English authors from the Botnar Research Centre (University of Oxford, Oxford, UK), Taylor PC, et al. (2021), it was noted that the mass production of recombinant monoclonal antibodies has already become fully viable and adequate to meet demand and is competitive with other treatment methods in terms of efficacy and cost. The use of neutralizing monoclonal antibodies can overcome the limitations of convalescent plasma therapy (CPT), including reducing the risk of blood-borne diseases, shortening the time required to produce high-affinity antibodies, and reducing the risk of insufficient antibody production. Furthermore, neutralizing monoclonal antibodies provide the high titer of neutralizing antibodies necessary for the effective treatment of donor plasma. Researchers and experts believe that there is a need for effective implementation into clinical practice, including the use of neutralizing mAbs and convalescent plasma for the treatment of SARS-CoV-2 [24].

Modern immunology data based on compiled universal libraries of mAbs obtained from healthy human donors offer the advantage of rapidly generating antibodies, regardless of material availability, from recovering patients during a pandemic. Researchers at the Braunschweig Institute of Biochemistry, Biotechnology, and Bioinformatics (Germany) presented data on the use of phage display to select SARS-CoV-2 spike antibodies from HAL9/10 native human antibody gene libraries and the subsequent identification of over 300 unique, fully human S1 antibodies. They found that 17 antibodies bind to the RBD, inhibiting spike binding to cells expressing ACE2 as scFv-Fc, and neutralize active SARS-CoV-2 infection of VeroE6 cells. The researchers showed that the STE73-2E9 antibody has the property of neutralizing active SARS-CoV-2 as IgG and binds to the ACE2-RBD interface in vitro [25].

Chinese researchers from the Laboratory of Microbial Physiological and Metabolic Engineering, CAS Institute of Microbiology, Chinese Academy of Sciences (Beijing, China) reported the isolation of two specific human monoclonal antibodies (designated CA1 and CB6) from a patient recovering from COVID-19. CA1 and CB6 demonstrated potent SARS-CoV-2-specific neutralizing activity in vitro. Administration of CB6 mAbs inhibited SARS-CoV-2 infection in rhesus macaques and was effective for therapeutic use. Structural studies showed that CB6 recognizes an epitope that overlaps with angiotensin-converting enzyme 2 (ACE2) binding sites in the SARS-CoV-2 receptor binding domain, thereby inhibiting virus-receptor interaction through both steric hindrance and direct competition for interface residues. According to the authors, mAb CB6 deserves further study as a candidate for clinical use [26].

High antiviral activity of a number of obtained mAb preparations was demonstrated in the work of researchers from the Section of Virology and the Department of Infectious Diseases and Immunology at Utrecht University (Utrecht, the Netherlands). In a publication by Wang C, et al. in 2020, a human monoclonal antibody that neutralizes SARS-CoV-2 (and SARS-CoV) in cell culture was reported [27]. To identify neutralizing SARS-CoV-2 antibodies, the researchers assessed the ELISA (cross-)reactivity of supernatants containing antibodies from a collection of 51 SARS-S hybridomas obtained from immunized H2L2 transgenic mice encoding chimeric immunoglobulins with human variable heavy and light chains and rat constant regions. Four mAbs from 50 SARS -S hybridoma supernatants were cross-reactive with the SARS2-S1 subunit by ELISA, of which one, 47D11, had neutralizing activity against SARS-S and SARS2-S pseudotyped VSV infection. The chimeric antibody 47D11 H2L2 was modified by the researchers into a fully human immunoglobulin by cloning the variable regions of the human heavy and light chains into the isotypic structure of human mesosomal globulin G1. The recombinantly expressed human antibody 47D11 was used by the researchers for further evaluation. According to the authors, this cloned cross-neutralizing antibody is tropic to the common epitope of such viruses and may have sufficient potential for the prevention and treatment of COVID-19 [27].

Researchers from the Institute of Cell and Organ Biology, Academia Sinica (Taipei, Taiwan), Su SC, et al. (2021) reported the generation and characterization of a series of chimeric antibodies against the receptor binding domain (RBD) of the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), [28]. Individual antibodies synthesized were capable of exhibiting exceptionally potent neutralizing activity in vitro and in vivo, and the most active of them targeted three different non-overlapping epitopes within the spike protein receptor binding domain (RBD), The receptor-binding domain of the spike protein (S) of the SARS-CoV-2 coronavirus (the virus that causes the COVID-19 epidemic), which is located on the S1 subunit of the S protein [28]. Cryoelectron microscopic analyses of two highly potent antibodies in complex with the SARS-CoV-2 spike protein showed that they may be particularly useful when combined in a cocktail therapy. The efficacy of this antibody cocktail was confirmed by researchers in mouse and hamster models of SARS-CoV-2 infection as a prophylactic and post-infection treatment. According to their data, with the emergence of more invasive, mutant variants of SARS-CoV-2, therapy with an antibody cocktail offers great promise for disease control and the prevention of the development of drug resistance [28].

Thus, studying the immunological structure of the COVID-19 virus and data from universal mAb libraries obtained from healthy human donors enabled rapid identification of the molecular structures of the spike protein (S) receptor binding domain and, using these structures, the generation of antibodies that specifically bind to the cellular angiotensin-converting enzyme 2 receptor and block the interaction of the virus with these protein structures in various cells and tissues of experimental animals. The efficacy of these mAbs and antibody cocktails was confirmed in cell and organ models of mice and hamsters infected with SARS-CoV-2, both as prophylactic and post-infection treatments. However, clinical evidence of their efficacy and safety is needed for their widespread implementation.

Clinical Trials to Evaluate the Efficacy of Monoclonal Antibody (mAb) Drugs in Outpatients for the Primary Prevention of COVID-19 Infection

The advent of innovative technologies in the etiotropic therapy of COVID-19 for the treatment of immunocompromised patients at high risk of severe coronavirus infection has opened up new perspectives in the treatment of the disease. The use of various virus-neutralizing mAbs for the treatment of coronavirus infection was approved by the FDA in 2020–2021 [4-6].

Bamlanivimab was the first monoclonal antibody approved for the treatment of COVID-19 (November 9, 2020) and received an EUA for the treatment of mild to moderate COVID-19 in adults and children aged 12 years (over 40 kg) and older who have tested positive for COVID-19 and in patients at high risk of progression to severe COVID-19 and/or requiring hospitalization [29]. The mAb bamlanivimab (LY-CoV555, LY3819253) is a neutralizing monoclonal antibody that targets the receptor-binding domain of the spike protein on the surface of the SARS-CoV-2 virus and works by blocking viral entry into cells [30] . It has undergone clinical trials as a drug against the COVID-19 virus [29].

In the Russian Federation, temporary approval is in effect for the use of combination mAbs (bamlavimab/etesivimab, casirivimab/imdevimab, cilgavimab/tixagevimab) and single-component (sotrovimab, regdanvimab) drugs based on recombinant human IgG1 monoclonal antibodies (mAbs) with direct antiviral action during the pandemic. All mAbs to SARS-CoV-2 are indicated for the treatment of adults and children (over 12 years of age) with mild to moderate COVID-19, are intended for use in outpatient or inpatient settings, and are most effective when administered as early as possible [31].

The efficacy of the mAb bamlanivimab in outpatients diagnosed with mild to moderate COVID-19 was assessed in several randomized, placebo-controlled trials, including the American BLAZE-1 study, conducted by researchers at the Department of Medicine, Lung Institute, and Cedars-Sinai Medical Center, Los Angeles (USA) [29]. The researchers hypothesized that virus-neutralizing monoclonal antibodies would reduce viral load, alleviate symptoms, and prevent disease progression, the development of respiratory complications, and reduce the need for hospitalization. They randomly assigned more than 450 patients diagnosed with mild to moderate COVID-19 to receive a single intravenous administration of the neutralizing antibody LY-CoV555 (bamlanivimab) in three doses ranging from 700 to 7000 mg versus placebo. The study assessed quantitative virological endpoints and clinical outcomes. Results were compared based on changes in viral load from baseline to 10 days. The data obtained in the study indicated a decrease in the logarithm of viral load by more than 3.5 times from baseline, which for the entire patient population corresponded to the elimination of more than 99% of viral RNA. Depending on the mAb dosages used, smaller differences compared to baseline were observed in patients receiving the drug at the minimum dose of 700 mg, as well as at the maximum dose of 7.0 g. The dose of 2.8 g proved optimal for the prevention of viral infection. Adverse effects of mAb therapy, deterioration of condition and the need for hospitalization or emergency department visits due to COVID-19 infection, amounted to 1.5% in the therapy group and more than 6.0% in the placebo group. The researchers

concluded that one of the three doses of bamlanivimab (neutralizing mAb LY-CoV555) appeared to enhance the natural decline in viral load over time, while the other doses did not accelerate this effect by day 10 after drug administration [29,32]

In another part of this American study, conducted by employees of Massachusetts General Hospital and Harvard Medical School in Boston Dougan M, et al. 2021, BLAZE-1 phase 3 in patients with newly diagnosed mild to moderate COVID-19 in outpatient settings and at high risk of progression to severe disease, the efficacy of a single intravenous administration of 2800 mg bamlanivimab and 2800 mg etesevimab (administered simultaneously), or placebo, was studied for 3 days after laboratory confirmation of the diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [33]. The researchers assessed the overall clinical status of patients, defined as COVID-19-related hospitalization or death from any cause within 30 days, in a sample of more than 1,000 randomized patients who received either bamlanivimab-etesevimab injections or placebo. The average patient age was over 50 years, but more than 50% were adolescents and women. At the end of the follow-up period, 2% of cases requiring hospitalization were associated with COVID-19 in the bamlanivimab-etesevimab group, compared with 7% in the placebo group. The relative risk difference was 70% and was significantly greater in the placebo group. There were no deaths in the group of patients with COVID-19 who received bamlanivimab-etesevimab injections, while the death rate in the comparison group was 1.7%. On day 7 of observation, patients receiving bamlanivimab and etesevimab injections demonstrated a greater change in log viral load from baseline than patients receiving placebo. The researchers concluded that mAb therapy with a combination of bamlanivimab and etesevimab in high-risk outpatients resulted in a reduction in COVID-19-related hospitalizations and deaths compared with placebo and also contributed to a reduction in SARS-CoV-2 viral load [33].

One of the fragments of the American multicenter randomized study BLAZE-1 was conducted by researchers from Baylor University Medical Center and the Scott & White Baylor Research Institute (Dallas, Texas, USA). The authors Gottlieb RL, et al. (2021), assessed the effect of bamlanivimab, as monotherapy or in combination with the mAb drug etesevimab, on viral load in patients with mild to moderate COVID-19 [34] . The study aimed to evaluate the effect of bamlanivimab monotherapy and combination therapy with bamlanivimab and etesevimab on viral load and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It included more than 610 patients with mild to moderate COVID-19 . Data from studies conducted at 49 US centers involved outpatients who tested positive for SARS-CoV-2 infection and had one or more mild to moderate symptoms. The study initially enrolled patients receiving bamlanivimab monotherapy or placebo, followed by an analysis of data from COVID-19 patients receiving bamlanivimab and etesevimab or placebo. All patients were randomized in groups of 100 to receive a single infusion of bamlanivimab at doses of 0.7, 2.8, or 7.0 g, while 110 patients received combination therapy with mAb drugs and injections of 2.8 g of bamlanivimab and 2.8 g of etesevimab. The placebo effect was assessed in 150 infected individuals. Changes in SARS-CoV-2 viral load were determined after 10 days of observation. Nine pre-specified secondary endpoints were examined dynamically, comparing each treatment group with placebo, as well as three viral load endpoints, five symptoms, and one clinical outcome (the proportion of patients with hospitalization, emergency department visits, or death on day 29 from COVID-19 complications). The researchers found that the change in the logarithm of viral load, compared with the baseline value on day 11 after the intervention, ranged from -3.5 to -4.1 times across the treatment dose groups (700, 2800, and 7000 mg). Of the secondary endpoints of treatment efficacy, differences between each treatment group and the placebo group were statistically significant for 10 parameters and symptoms out of 84 endpoints.

The percentage of patients admitted to hospital or visiting the emergency department due to COVID-19 was 5.8% in the placebo group and was significantly lower (0.9-2.0%) in the groups with different dosages of the drug and 0.9% in the combination therapy group. Among the side effects of mAb therapy, the researchers noted an immediate hypersensitivity reaction, which was recorded in 9 patients (6 in the bamlanivimab group, 2 in the combination therapy group, and 1 in the placebo group). There were no fatal cases during the study. The authors concluded that among outpatients with mild to moderate COVID-19, treatment with bamlanivimab and etesevimab, compared with placebo, was accompanied by a statistically significant reduction in SARS-CoV-2 viral load, when analyzed after 11 days; and with bamlanivimab monotherapy alone, no significant difference in viral load reduction was observed. Researchers believe it is promising to conduct clinical trials to evaluate the efficacy of anti-spike-neutralizing monoclonal antibodies in patients not only for the prevention of disease progression in outpatient settings, but also in inpatient settings in hospitalized patients with severe complications of COVID-19 [34].

The REGN-COV2, a multicenter, American study of a neutralizing antibody cocktail in outpatients with COVID-19, was designed to evaluate the efficacy of combination therapy with mAb drugs in outpatients with COVID-19. The study was organized and coordinated by R. Pharmaceuticals (Tarrytown, NY, USA) [35]. To achieve the study objectives, all patients were randomized to receive placebo or a low- or high-dose REGN-COV2 mAb. The study included individuals aged 18 years or older and with no indications for inpatient treatment. All patients had confirmed SARS-CoV-2 infection, with a positive SARS-CoV-2 test result prior to randomization and the presence of viral symptoms that appeared no later than 7 days prior to randomization. The efficacy of mAbs was initially assessed in a subgroup of patients who tested negative for three antibodies: IgA, IgG against the S1 domain of the spike protein, and IgG against the nucleocapsid protein. Those who tested positive were randomized as having antibodies to the virus. A mAb cocktail of antibodies from the REGN-COV2 drug, which contains casirivimab (REGN10933) and imdevimab (REGN10987), was administered intravenously at equal doses as part of the mixture. All subjects underwent serum antibody testing to SARS-CoV-2 and measurement of the two components of REGN-COV2 in their serum.

We evaluated two human neutralizing monoclonal antibodies against the spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) used in a combination cocktail (REGN-COV2) to reduce the risk of the emergence of treatment-

resistant mutant viruses. The analysis included data from a sample of 275 patients. We found that in the REGN-COV2 combination dose groups, compared with placebo, the change in viral load was -0.55 log 10 copies/mL of the drug, adjusted for treatment time, and among patients with a negative serum antibody test result at baseline, it was 27% lower (-0.40 log). In the overall study population, 6% of patients in the placebo group and 3% of patients in the REGN-COV2 combination dose groups required a doctor's consultation (visit) for symptoms of the disease, such as hypothermia and rhino-broncho-pulmonary symptoms, while in the group with a negative serum antibody test result at baseline, the corresponding symptoms and need for consultation were 15% and 6%, with this difference being significant. The percentage of patients with hypersensitivity reactions, infusion-related reactions, and other adverse events was similar in the REGN-COV2 combination dose and placebo groups. The researchers concluded that the REGN-COV2 antibody cocktail reduced viral load, with a more pronounced effect observed in patients in whom the immune response had not yet been initiated or who had a high viral load at baseline [35].

Another fragment of the multicenter American REGEN-COV study was presented in a publication by its coordinators, employees of the Department of Medicine and Microbiology at the University of Pennsylvania (Philadelphia, USA) O'Brien et al. (2021), [36] . According to the study results, it was noted that the combination of monoclonal antibodies casirivivimab and imdevimab significantly reduced the risk of hospitalization or death among individuals at high risk of infection with coronavirus disease 2019 (COVID-19), but the possibility of preventing infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the subsequent development of COVID-19 in individuals at high risk of infection who had household contact with a SARS-CoV-2 carrier using subcutaneous administration of this REGEN-COV mAb combination needed to be verified and clarified. Researchers randomized patients aged 12 years and older to the study within 96 hours of household contact with individuals diagnosed with SARS-CoV-2. Patients were randomized to receive either the REGEN-COV mAb or placebo via subcutaneous injection. The endpoints for evaluating efficacy were the development of symptomatic SARS-CoV-2 infection by day 28 in participants who did not have SARS-CoV-2 infection, confirmed by quantitative reverse transcriptase polymerase chain reaction (RT-PCR) or baseline seronegativity. In this study , symptomatic SARS-CoV-2 infection developed in only 1.5% of patients treated with the REGEN-COV mAb and was relatively more frequent—7.8% in the placebo group—with a significant relative risk reduction of 80%. Between the 2nd and 4th weeks after mAb administration, the relative reduction in disease risk was greater than 90%. The REGEN-COV cocktail also prevented symptomatic and asymptomatic infection in the group as a whole, with a relative risk reduction of more than 60%.

Administration of the drug to infected patients was accompanied by a reduction in the time to symptom resolution—2 weeks shorter than with placebo—and the duration of high viral load was significantly shorter. The authors did not observe an increase in toxic effects with increasing REGEN-COV dose. They concluded that administration of the REGEN-COV vaccine prevented symptomatic COVID-19 infection and asymptomatic SARS-CoV-2 infection in previously uninfected individuals who had contact with infected individuals at home, and shortened the duration of the disease and the period of high viral load in infected patients [36].

A press release from Roche summarized the results of the REGN-COV 2067 study in high-risk, non-hospitalized COVID-19 patients. The study data showed that the mAb casirivivamab and imdevimab, part of Ronapreve, improved survival in high-risk, non-hospitalized COVID-19 patients by reducing the risk of hospitalization and death. Ronapreve is also used to treat COVID-19 in adults, adolescents, and children aged 2 years and older and weighing at least 10 kilograms who do not require supplemental oxygen and who are at increased risk of developing severe disease. Furthermore, its ability to retain activity against new virus variants, including the Delta variant, which had been demonstrated in preclinical studies, was demonstrated [37].

The Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) has issued a scientific opinion under Article 5(3) of Regulation (EC) No 726/2004, supporting the use of casirivimab and imdevimab as a treatment option for patients with confirmed COVID-19 who do not require oxygen therapy and who are at high risk of developing severe COVID-19. A Phase II/III study has shown that Ronapreve™ (casirivimab and imdevimab) significantly reduces viral load in patients hospitalized with COVID-19. [37].

In the United States, the Food and Drug Administration (FDA) approved REGEN-COV monoclonal antibody therapy for post-exposure prophylaxis (prevention) of COVID-19 in a statement on August 10, 2021 [38].

Japan was the first country to approve Ronapreve (casirivivamab and imdevimab) for the treatment of mild to moderate COVID-19. The Japanese Ministry of Health, Labor, and Welfare (MHLW) based its recommendation on the results of the global phase III REGN-COV 2067 study in high-risk, non-hospitalized COVID-19 patients, which showed that casirivivamab and imdevimab reduced hospitalization or mortality by 70% and the duration of symptoms by four days, as well as the results of a phase I clinical trial that examined the safety, tolerability, and pharmacokinetics of this mAb in Japanese patients [39].

The mAb AZD7442, a combination of human monoclonal antibodies, was developed in the United States by Vanderbilt University Medical Center in Nashville, Tennessee. AZD7442 is a combination of two long-acting antibodies (LAAs), tixagevimab and cilgavimab, derived from B cells of patients who have recovered from SARS-CoV-2 infection. It has proven effective in outpatients for the prevention and reduction of disease severity in symptomatic COVID-19. [40]. This monoclonal antibody combination has been shown to reduce the incidence of symptomatic COVID-19 cases by 77% compared to placebo. In the Phase III Provent study, a randomized, double-blind, placebo-controlled study involving more than 5,000 people. There were no cases of severe disease or death among patients taking the drug. A decrease in the immune response to vaccination was detected in more than 75% of study participants who suffered from comorbidities. During this

study, the effectiveness of the drug AZD7442 was studied at 87 centers in the United States, Great Britain, Spain, France, and Belgium. During the study, more than 5,000 adult patients were randomized to receive a single dose of AZD7442 300 mg (3,500 people) or a placebo - an injection of sterile saline (1,700 people). In the intervention group, more than 40% of patients were 60 years of age and older, and more than 75% had comorbidities. The analysis was conducted after 6 months. showed that a single dose of AZD7442 reduced the risk of developing symptomatic COVID-19 by 80% compared to placebo. Participants receiving the mAb combination drug did not experience any cases of severe COVID-19 or COVID-19-related deaths at either the primary or six-month follow-up, while five cases of severe COVID-19 and two deaths were reported in the placebo group [41].

Another international, randomized, double-blind, placebo-controlled study of this mAb drug AZD7442 (tixagevimab-cilgavimab), called Tackle, coordinated by staff at the Department of Primary Care at the University of Oxford (Oxford, UK), aimed to evaluate the safety and efficacy of a single 600 mg injection of the drug (in the Provent study, a single 300 mg injection, half as much), compared with placebo in non-hospitalized adults with mild to moderate COVID-19, with symptoms of the disease for less than seven days. The study included almost 900 participants, randomized to receive AZD7442 or placebo (450 people). In the intervention group, only about 10% of participants were 65 years and older, but 90% had comorbidities and conditions associated with a high risk of developing severe variants of COVID-19. In an analysis, 30 days after administration of AZD7442, researchers observed a greater than 85% reduction in the risk of developing severe COVID-19 or death (from any cause) compared with placebo in patients who had symptoms for three days or less at the time of treatment initiation [42,43].

Thus, the use of a combination of neutralizing monoclonal antibodies casirivivimab and imdevimab in the randomized, placebo-controlled BLAZE-1 and REGEN-COV trials was associated with a reduction in viral load and hospitalization rates in hospitals and emergency departments among outpatients with coronavirus disease 2019 (COVID-19). In the Provent and Tackle trials, using the mAb AZD7442, consisting of two long-acting antibodies (LAAs), tixagevimab and cilgavimab, a greater than 85% reduction in the risk of developing severe COVID-19 or death (from any cause) in outpatients was observed compared with placebo, which characterizes its high antiviral activity.

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Reference

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