УДК 616.988-08:578.834.1
DOI: https://doi.org/10.17816/RFD108485

Этиотропная терапия новой коронавирусной инфекции. Ожидания и реалии. Часть 2

О.Ю. Кузнецова

Северо-Западный государственный медицинский университет им. И.И. Мечникова, Санкт-Петербург, Россия

Вторая часть обзора включает анализ данных литературы, посвященных этиотропной терапии новой коронавирусной инфекции с использованием препаратов из групп моноклональных антител и ингибиторов вирусной протеазы. Подчеркнута сложность выбора препарата для лечения новой коронавирусной инфекции, вызванной штаммом омикрон, из-за высокой степени мутации этого штамма. Описан механизм действия комбинированного препарата Паксловид, состоящего из нирматрелвира и ритонавира, приведены данные о его высокой эффективности и безопасности, полученные в рандомизированных многоцентровых плацебо-контролируемых исследованиях. Обращено внимание на рекомендации Всемирной организации здравоохранения по применению данного препарата лицами с высоким риском тяжелого течения новой коронавирусной инфекции, и отмечена необходимость ранней диагностики клинических симптомов заболевания для своевременного назначения этиотропной терапии.

Ключевые слова: новая коронавирусная инфекция; COVID-19; амбулаторная практика; этиотропное лечение; моноклональные антитела; бамланивимаб и этесевимаб; казиривимаб и имдевимаб; сотровимаб; нирматрелвир и ритонавир; эффективность лечения; побочное действие.

Как цитировать:
Кузнецова О.Ю. Этиотропная терапия новой коронавирусной инфекции. Ожидания и реалии. Часть 2 // Российский семейный врач. 2022. Т. 26. № 2. С. 7–12. DOI: https://doi.org/10.17816/RFD108485

Рукопись получена: 02.06.2022 **Рукопись одобрена:** 16.06.2021 **Опубликована:** 30.06.2022

DOI: https://doi.org/10.17816/RFD108485

Etiotropic therapy of the new coronavirus infection. Expectations and realities. Part 2

Olga Yu. Kuznetsova

North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

Part 2 of the review includes an analysis of the literature data related to the etiotropic therapy of a new coronavirus infection using drugs from the group of monoclonal antibodies and viral protease inhibitors. The difficulty of choosing a drug for the treatment of a new coronavirus infection caused by the Omicron strain due to the high degree of mutation is emphasized. The mechanism of action of the combined drug Paxlovid, consisting of nirmatrelvir and ritonavir, is described, data on its high efficacy and safety obtained in randomized multicenter placebo-controlled trials are presented. Attention is drawn to the World Health Organization recommendations on the use of this drug in people at high risk of a severe course of a new coronavirus infection and the need for early diagnosis of clinical symptoms for the timely appointment of etiotropic therapy.

Keywords: new coronavirus infection; COVID-19; outpatient practice; etiotropic treatment; monoclonal antibodies; bamlanivimab and etesevimab; casirivimab and imdevimab; sotrovimab; nirmatrelvir and ritonavir; treatment efficacy; side effects.

To cite this article:
Kuznetsova OYu. Etiotropic therapy of the new coronavirus infection. Expectations and realities. Part 2. *Russian Family Doctor.* 2022;26(2):7–12. DOI: https://doi.org/10.17816/RFD108485

Received: 02.06.2022 **Accepted:** 16.06.2022 **Published:** 30.06.2022

BACKGROUND

The development of new etiotropic drugs aimed at combating coronavirus disease-2019 (COVID-19) remains an urgent problem. As indicated in Part 1 of the review, the drugs included in the clinical guidelines for the treatment of COVID-19 and approved by the World Health Organization (WHO) cause several adverse events, and their efficiency was questioned in some publications. Therefore, the emergence of new drugs with different mechanisms of action is of interest to clinical practice.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is constantly mutating, which induces the emergence of new strains. The WHO currently lists the delta strain (first identified in India in December 2020) and the omicron strain (first reported in South Africa in November 2021) as variants of concern. In its information bulletins, the WHO emphasizes that omicron continues to mutate, and the genomic profiles of its new variants differ significantly from those of the first lines of the BA.1 variant [1]. A comparative study of the protective effects of vaccination depending on the causative virus strain showed that the neutralizing activity of antibodies developed after the vaccination is much higher in the delta strain than in the omicron strain, even after booster doses [2]. This circumstance indicates the need to expand the search for new classes of etiotropic drugs that are efficient in the treatment of COVID-19.

One of the search directions for such agents was the study of the virus-neutralizing effect of artificial monoclonal antibodies against SARS-CoV-2 at the end of 2021. Recombinant human monoclonal antibodies of the IgG1 class, by binding to epitopes of the receptor-binding domain of the S-protein, block its interaction with angiotensin-converting enzyme 2 (ACE2), which suppresses the entry of the virus into cells and ceases its replication. Currently, single-component monoclonal antibodies (sotrovimab) and combined drugs of the same group (bamlanivimab and etesevimab, casirivimab and imdevimab) are recommended for the treatment of COVID-19 [3]. However, the WHO document "Drug Therapy for COVID-19" emphasizes that the combination of casirivimab and imdevimab is indicated for outpatient use only in people at high risk of severe COVID-19 requiring hospitalization [4].

The listed drugs have not yet been registered in Russia, but the Russian Ministry of Health issued permission to use both single-component and combined monoclonal antibodies during the pandemic, in accordance with Decree of the Government of the Russian Federation dated April 3, 2020, No. 441, which stated special conditions for the circulation of medicinal drugs intended for use in emergencies, including for the treatment and prevention of diseases that pose a danger for the wider public [5].

SOTROVIMAB

The neutralizing activity of monoclonal antibodies in various variants of the omicron strain, which became the predominant causative agent of COVID-19 worldwide in 2022, remains a fundamentally important issue. Preclinical studies have concluded that among monoclonal antibodies tested, including bamlanivimab, casirivimab, cilgavamab, imdevimab, sotrovimab, and tixagevimab, only sotrovimab demonstrated the ability to neutralize significantly the omicron strain *in vitro* [6].

The recommended dose of sotrovimab is 500 mg in 0.9% sodium chloride solution. In healthcare settings where patients can be monitored during and at least 1 h after administration, it should be administered for 5 days after the onset of COVID-19 symptoms. Sotrovimab is recommended for adult patients at high risk of severe COVID-19 requiring hospitalization.

According to the phase II and III multicenter, double-blind, placebo-controlled study COMET-ICE (NCT04545060), sotrovimab reduces the risk of disease progression in non-hospitalized adults with mild-to-moderate COVID-19 and at a high risk of disease progression to severe COVID-19. The study included patients aged ⩾18 years with SARS-CoV-2 infection confirmed by polymerase chain reaction or antigen testing. Symptoms developed in all patients within 5 days before randomization, and they had at least one risk factor for severe COVID-19, namely, aged ⩾55 years, diabetes mellitus, obesity (body mass index >30 kg/m^2), chronic kidney disease (estimated glomerular filtration rate < 60 mL/min/1.73 m^2), chronic heart failure (New York Heart Association classes II–IV), chronic obstructive pulmonary disease or moderate or severe bronchial asthma. Patients with symptoms of severe COVID-19 (i.e., dyspnea at rest, oxygen saturation <94%, or need for supplemental oxygenation) were not enrolled in the study. Treatment was performed for 3 and 4–5 days after the onset of COVID-19 symptoms in 59% and 41% of the patients, respectively. The proportion of patients requiring hospitalization for any reason after ⩾24 h or died from any cause within 29 days (primary endpoint) was 1% in the sotrovimab group and 6% in the placebo group, which was considered significant ($p < 0.001$) with relative risk reduction of 79% (95% CI 50–91). By day 29, no lethal outcomes were observed in the sotrovimab group, and two patients died in the placebo group. The most common adverse event in the main group was diarrhea (in 2% of cases). The incidence of systemic infusion reactions (including hypersensitivity reactions) was low, similar to the main and control groups (1% of patients in each group) [7].

Russia allowed the use of sotrovimab [8]. However, a study of its efficiency as an antiviral agent for the treatment of COVID-19 caused by various variants of the omicron

strains showed less impressive results. Aleem et al. noted that the omicron B.1.1.529 variant had numerous mutations in the spike protein, which reduces its susceptibility to monoclonal antibodies *in vitro*. Sotrovimab retains its activity against omicron BA.1 and BA.1.1 subvariants, but its activity is reduced against omicron VA.2 variant [9].

Since this omicron variant is the main circulating variant in the USA, sotrovimab is not included in the USA clinical guidelines for the treatment of COVID-19 [10].

PAXLOVID

A new direction in antiviral drug development is the creation of agents that can cease viral replication in the human body by affecting the protease enzyme. Nirmatrelvir is a new type of 3C-like protease (3CL) inhibitor, an enzyme necessary for the SARS-CoV-2 virus functioning and replication. Nirmatrelvir is combined with ritonavir, an inhibitor of cytochrome P_{450} CYP3A4, which increases the concentration of nirmatrelvir to achieve the targeted therapeutic effect. Previously, ritonavir was used to enhance the action of the protease inhibitors (a viral protease) of the human immunodeficiency virus. The complex consisting of these drugs is produced under the name Paxlovid.

An interim analysis of data from phase II and III clinical trials conducted by Pfizer, involving 1,219 adult patients enrolled up to September 29, 2021, showed that among patients treated within 3 days of the onset of COVID-19 symptoms, the risk of hospitalization associated with COVID-19 and deaths from any cause were 89% lower in the Paxlovid group than in the placebo group [11]. Based on these positive results, as well as the recommendations of the independent study data-monitoring committee and the US Food and Drug Administration, enrollment in the study was terminated. In total, 70% of 3,000 (planned) patients from clinical trial centers in the Americas, Europe, Africa, and Asia were included, in which 45% of the patients were from the USA. The patients were randomized in a 1:1 ratio; half of them received Paxlovid, whereas the other half received placebo orally every 12 h for 5 days. Moreover, 0.8% (3/389) of the patients treated with Paxlovid within 3 days of symptom onset were hospitalized within 28 days of randomization, and no lethal outcomes were registered. Furthermore, 7% (27/385) of the patients who received placebo were hospitalized, of which seven died. The significance of these results was assessed as high ($p < 0.0001$). Similar data were noted in patients treated within 5 days after the onset of symptoms, where 1% (6/607) of the patients in the Paxlovid group (no lethal outcomes) and 6.7% (41/612) of the patients in the placebo group (10 lethal outcomes) were hospitalized before day 28. In general, up to day 28, no deaths were recorded in the Paxlovid group, whereas 10 (1.6%) patients died in the placebo group. To examine the drug's safety, data from 1,881 patients were analyzed. The proportions of adverse events in the groups were comparable, that is, 19% in the Paxlovid group and 21% in the placebo group, and most of the adverse effects were mild. Patients in the antiviral group were less likely to experience serious side effects (1.7% vs. 6.6% in the placebo group) or discontinue the study because of side effects (2.1% vs. 4.1%) than those in the control group.

Hammond et al. examined 2246 patients (Paxlovid group, $n = 1120$; placebo group, $n = 1126$) [12]. In a planned interim analysis of the parameters of patients treated within 3 days of symptom onset, the rate of hospitalizations or lethal outcomes associated with COVID-19 was lower in the Paxlovid group than in the placebo group by 6.32 percentage points on day 28 (relative risk reduction by 89.1%). No lethal outcomes occurred in the Paxlovid group, whereas seven patients died in the placebo group. The viral load was lower in the main group than in the placebo group on day 5 of treatment with an adjusted mean difference of –0.868 log10 copies per milliliter if treatment was initiated within 3 days of symptom onset. During the treatment period, the incidence of any adverse events was comparable between the two groups, namely, 22.6% in the Paxlovid group and 23.9% in the placebo group. Dysgeusia (5.6% vs. 0.3%) and diarrhea (3.1% vs. 1.6%) were more common with Paxlovid than with the placebo. Treatment of symptomatic COVID-19 with Paxlovid resulted in an 89% reduction in the risk of progressing to severe COVID-19 compared with placebo, with no apparent safety concerns.

Based on research data, the WHO has recommended nirmatrelvir and ritonavir marketed as the combination drug Paxlovid for the treatment of patients with mild or non-severe COVID-19 but at high risk of hospitalization. Pfizer's oral antiviral drug is suitable for patients who are most at risk of severe COVID-19 requiring hospitalization. This group includes unvaccinated and older patients and those taking immunosuppressive drugs. According to the WHO, in the treatment of patients with a low hospitalization risk, the benefit of Paxlovid will be insignificant because Paxlovid is recommended for use only in the initial disease stages; therefore, it is very important to expand the possibilities for early diagnostics [13].

N.B. In Part 1 of the review, remdesivir was reported to be removed from the list of drugs recommended by the WHO for the treatment of COVID-19, since the data at that time indicated that this drug had little or no effect on mortality. A few studies, in particular the work by Gottlieb et al., have demonstrated the efficiency of remdesivir in non-hospitalized patients at high risk of COVID-19 progression. With an acceptable safety profile, there was an 87% reduction in the risk of hospitalization or death in the remdesivir group compared with the results in the placebo group [14]. According to data as of April 21, 2022, the WHO has updated

its recommendation for the use of remdesivir. Following the publication of information from a new clinical trial, the WHO suggests the use of remdesivir for mild-to-moderate COVID-19 if the patient is at high risk of hospitalization [15].

CONCLUSION

Strategies to reduce and block the spread of SARS-CoV-2 infection and COVID-19 development are the subject of thousands of studies worldwide. Not all drugs recommended at the onset of the pandemic met expectations and saved the lives of patients with serious diseases. The ability of the virus, specifically the omicron strain, to mutate constantly determined the low efficiency of monoclonal antibodies, which demonstrated a good treatment effect on COVID-19 cases caused by previous strains.

Paxlovid, which mainly inhibits the protease enzyme with timely disease detection, can help reduce the risk of severe COVID-19 and the need for hospitalization in patients at risk. The impressive results obtained in clinical trials must be confirmed in clinical practice, often leveling the final results of using even the most effective drugs. Thus, it is necessary to accumulate, analyze, and publish data on the use of this antiviral agent in various categories of patients, which will enable full evaluation of the efficiency of drugs that have attained merit from the WHO and national healthcare systems of countries where these drugs are available.

ADDITIONAL INFORMATION

Funding. The preparation of the publication did not have financial support or sponsorship.

Conflict of interest. The author declare no conflict of interest.

The author has prepared a scientific literature review, that became the basis of the article, read, and approved the final version before its publication.

ДОПОЛНИТЕЛЬНО

Источник финансирования. Подготовка публикации не имела финансового обеспечения или спонсорской поддержки.

Конфликт интересов. Автор декларирует отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Автор подготовила научный обзор литературы, на основании которого была написана статья, прочла и одобрила финальную версию перед публикацией.

REFERENCES

1. Otslezhivanie variantov virusa SARS-CoV-2 [Internet]. *WHO.* Available from: https://www.who.int/ru/activities/tracking-SARS-CoV-2-variants. Accessed: June 2, 2022. (In Russ.)

2. Hoffmann M, Krüger N, Schulz S, et al. The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic. *Cell*. 2022;185(3):447–456.e11. DOI: 10.1016/j.cell.2021.12.032

3. Vremennye metodicheskie rekomendatsii. Diagnostika, profilaktika i lechenie novoi koronavirusnoi infektsii (COVID-19), versiya 14 (27.12.2021) [Internet]. Available from: https://xn--80aesfpebagmfblc0a.xn--p1ai/ai/doc/1213/attach/vmr_COVID-19_V14_27-12-2021.pdf. Accessed: June 2, 2022

4. Lekarstvennaya terapiya pri COVID-19. Variativnye rekomendatsii. 24.09.2021 [Internet]. Available from: https://apps.who.int/iris/bitstream/handle/10665/345356/WHO-2019-nCoV-therapeutics-2021.3-rus.pdf. Accessed: June 2, 2022. (In Russ.)

5. Postanovlenie Pravitel'stva Rossiiskoi Federatsii ot 03.04.2020 No. 441 [Internet]. Ofitsial'nyi internet-portal pravovoi informatsii (pravo.gov.ru). Available from: http://publication.pravo.gov.ru/Document/View/0001202004060038. Accessed: June 2, 2022. (In Russ.)

6. Heo YA. Sotrovimab: First Approval. *Drugs.* 2022;82(4):477–484. DOI: 10.1007/s40265-022-01690-7

7. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of the neutralizing SARS-CoV-2 antibody sotrovimab in preventing progression of COVID-19: a randomized clinical trial. *medRxiv*. 2021. DOI: 10.1101/2021.11.03.21265533

8. Spravochnik lekarstvennykh sredstv VIDAL [Internet]. Available from: https://www.vidal.ru/novosti/preparat-sotrovimab-dlya-lecheniya-covid-19-legkoj-i-srednej-stepeni-tyazhesti-u-patsientov-10462. Accessed: June 2, 2022. (In Russ.)

9. Aleem A, Akbar Samad AB, Slenker AK. Emerging variants of SARS-CoV-2 and novel therapeutics against coronavirus (COVID-19). 2022 May 12. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.

10. COVID-19 Treatment Guidelines [Internet]. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/?utm_source=site&utm_medium=home&utm_campaign=highlights. Accessed: June 2, 2022.

11. Mahase E. Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports. *BMJ.* 2021;375:n2713. DOI: 10.1136/bmj.n2713

12. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. *N Engl J Med.* 2022;386(15):1397–1408. DOI: 10.1056/NEJMoa2118542

13. VOZ rekomenduet k primeneniyu effektivnoe lekarstvo ot COVID-19 [Internet]. *WHO.* Available from: https://news.un.org/ru/story/2022/04/1422402. Accessed: June 2, 2022. (In Russ.)

14. Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med.* 2022. Vol. 386, No. 4. 305–315. DOI: 10.1056/NEJMoa2116846

15. WHO recommends against the use of remdesivir in COVID-19 patients [Internet]. Available from: https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients. Accessed: June 2, 2022.

СПИСОК ЛИТЕРАТУРЫ

1. Отслеживание вариантов вируса SARS-CoV-2 [Электронный ресурс] // ВОЗ. Режим доступа: https://www.who.int/ru/activities/tracking-SARS-CoV-2-variants. Дата обращения: 02.06.2022.
2. Hoffmann M., Krüger N., Schulz S. et al. The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic // Cell. 2022. Vol. 185, No. 3. P. 447–456.e11. DOI: 10.1016/j.cell.2021.12.032
3. Временные методические рекомендации. Диагностика, профилактика и лечение новой коронавирусной инфекции (COVID-19), версия 14 (27.12.2021) [Электронный ресурс]. Режим доступа: https://xn--80aesfpebagmfblc0a.xn--p1ai/ai/doc/1213/attach/vmr_COVID-19_V14_27-12-2021.pdf. Дата обращения: 02.06.2022.
4. Лекарственная терапия при COVID-19. Вариативные рекомендации. 24.09.2021 [Электронный ресурс]. Режим доступа: https://apps.who.int/iris/bitstream/handle/10665/345356/WHO-2019-nCoV-therapeutics-2021.3-rus.pdf. Дата обращения: 02.06.2022.
5. Постановление Правительства Российской Федерации от 03.04.2020 № 441 [Электронный ресурс] // Официальный интернет-портал правовой информации (pravo.gov.ru). Режим доступа: http://publication.pravo.gov.ru/Document/View/0001202004060038. Дата обращения: 02.06.2022.
6. Heo Y.A. Sotrovimab: First Approval // Drugs. 2022. Vol. 82, No. 4. P. 477–484. DOI: 10.1007/s40265-022-01690-7
7. Gupta A., Gonzalez-Rojas Y., Juarez E. et al. Effect of the neutralizing SARS-CoV-2 antibody sotrovimab in preventing progression of COVID-19: a randomized clinical trial // medRxiv. 2021. DOI: 10.1101/2021.11.03.21265533
8. Справочник лекарственных средств VIDAL [Электронный ресурс]. Режим доступа: https://www.vidal.ru/novosti/preparat-sotrovimab-dlya-lecheniya-covid-19-legkoj-i-srednej-stepeni-tyazhesti-u-patsientov-10462. Дата обращения: 02.06.2022.
9. Aleem A., Akbar Samad A.B., Slenker A.K. Emerging variants of SARS-CoV-2 and novel therapeutics against coronavirus (COVID-19). 2022 May 12. // StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.
10. COVID-19 Treatment Guidelines [Электронный ресурс]. Режим доступа: https://www.covid19treatmentguidelines.nih.gov/therapies/anti-sars-cov-2-antibody-products/anti-sars-cov-2-monoclonal-antibodies/?utm_source=site&utm_medium=home&utm_campaign=highlights. Дата обращения: 02.06.2022.
11. Mahase E. Covid-19: Pfizer's paxlovid is 89% effective in patients at risk of serious illness, company reports // BMJ. 2021. Vol. 375. P. n2713. DOI: 10.1136/bmj.n2713
12. Hammond J., Leister-Tebbe H., Gardner A. et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19 // N. Engl. J. Med. 2022. Vol. 386, No. 15. P. 1397–1408. DOI: 10.1056/NEJMoa2118542
13. ВОЗ рекомендует к применению эффективное лекарство от COVID-19 [Электронный ресурс]. Режим доступа: https://news.un.org/ru/story/2022/04/1422402. Дата обращения: 02.06.2022.
14. Gottlieb R.L., Vaca C.E., Paredes R. et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients // N. Engl. J. Med. 2022. Vol. 386, No. 4. P. 305–315. DOI: 10.1056/NEJMoa2116846
15. WHO recommends against the use of remdesivir in COVID-19 patients [Электронный ресурс]. Режим доступа: https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients. Дата обращения: 02.06.2022.

AUTHOR INFO

Olga Yu. Kuznetsova, MD, Dr. Sci. (Med.), Professor;
address: 41 Kirochnaya St., Saint Petersburg, 191015, Russia;
ORCID: https://orcid.org/0000-0002-2440-6959;
Scopus Author ID: 24448739500; eLibrary SPIN: 7200-8861;
ResearcherId: O-4056-2014; e-mail: oukuznetsova@mail.ru

ОБ АВТОРЕ

Ольга Юрьевна Кузнецова, д-р мед. наук, профессор;
адрес: Россия, 191015, Санкт-Петербург, Кирочная ул., д. 41;
ORCID: https://orcid.org/0000-0002-2440-6959;
Scopus Author ID: 24448739500; eLibrary SPIN: 7200-8861;
ResearcherId: O-4056-2014; e-mail: oukuznetsova@mail.ru