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Этиотропная терапия новой коронавирусной инфекции: ожидания и реалии в начале 2022 года. Часть 1

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Обзор включает анализ последних данных литературы об этиотропной терапии новой коронавирусной инфекции. Поиск эффективного противовирусного лечения этого заболевания продолжается. Нередко экстренная необходимость в наличии специфического этиотропного препарата становилась причиной тестирования лекарств без фармакологического обоснования и общепринятой процедуры многоэтапных клинических испытаний. Из-за этого многие клинические исследования, включающие тысячи пациентов, не продемонстрировали высокую эффективность и безопасность препаратов, выбранных в качестве этиотропной терапии. В данном обзоре мы рассмотрели препараты, которые достаточно подробно исследованы, описаны в международных изданиях, а также включены в российские методические рекомендации для использования в амбулаторных условиях: фавипиравир и молнупиравир. Их механизмы действия, эффективность и возможные побочные эффекты изучены при клинических испытаниях, результаты которых находятся в открытом доступе, что позволило оценить целесообразность их применения в реальной клинической практике.

Ключевые слова: новая коронавирусная инфекция; амбулаторная практика; этиотропное лечение; фавипиравир; молнупиравир; эффективность лечения; побочное действие.

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Etiotropic therapy of the new coronavirus infection: expectations and realities at the beginning of 2022. Part 1

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The review includes an analysis of the latest literature data on the etiotropic therapy of a new coronavirus infection. The search for an effective antiviral treatment for SARS-CoV-2 infection is ongoing. Often, the urgent need for an antiviral drug was a pretext for testing drugs without pharmacological justification, bypassing the generally accepted procedure for conducting multi-stage clinical trials. In this regard, many clinical trials involving thousands of patients did not demonstrate the high efficacy and safety of drugs that were chosen as etiotropic therapy. In this review, we focused on the efficacy and safety of those drugs that have been studied in sufficient detail, which are reflected in international publications, and are also included in Russian guidelines for use on an outpatient practice: favipiravir and molnupiravir. The mechanism of action of antiviral drugs, their effectiveness and possible side effects were studied in clinical trials, the results of which are in the open press, which made it possible to analyze these drugs in terms of the appropriateness of their use in real clinical practice.

Keywords: new coronavirus infection; outpatient practice; etiotropic treatment; favipiravir; molnupiravir; treatment efficacy; side effects.

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ECO•VECTOR

BACKGROUND

The search for an effective etiotropic treatment for the novel coronavirus disease 2019 (COVID-19) still continues. The urgent need for an antiviral drug was often the reason for drug testing without pharmacological justification and the generally accepted procedure for multistage clinical trials. Thus, many clinical studies involving thousands of patients have not demonstrated high efficacy and safety of the drugs chosen as etiotropic therapy.

At the start of the pandemic, researchers focused primarily on the study of already existing antiviral and anti-inflammatory drugs, such as the following [1–3]:

- Hydroxychloroquine, which has been successfully used in the treatment of malaria and rheumatology.
- Remdesivir developed as an antiviral agent against RNA viruses, in particular the Ebola virus.
- Lopinavir and ritonavir used to treat human immunodeficiency virus infection.

They were included in the Russian temporary guidelines for diagnostics, prevention, and treatment of COVID-19 [4]. However, their use fell short of expectation, since they did not influence either the intermediate points (acceleration of virus elimination) or the final points (decrease in mortality). When the side effects of these drugs were reported, which were especially significant for patients with concomitant cardiovascular diseases, diabetes mellitus, and liver and kidney diseases [5], the World Health Organization announced the termination of the study of hydroxychloroquine, lopinavir, and ritonavir as etiotropic therapy for COVID-19 [6]. Hydroxychloroquine was also subsequently excluded from recommendations in Russia, as were lopinavir and ritonavir [7]. Remdesivir, despite the recommendation of the World Health Organization to exclude it from the list of drugs for the treatment of COVID-19 [8, 9], remains a drug that can be taken under inpatient treatment [10].

Development works aimed at the analysis of the clinical efficacy and safety of drugs for the etiotropic therapy of COVID-19 are being conducted throughout the pandemic. Despite advances in vaccine creation, vaccination may be limited because of contraindications, and the rapidly mutating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may partially overcome the effects of vaccines that target strains of the virus that were common at the pandemic onset, as in the omicron strain [11].

FAVIPIRAVIR

Favipiravir is one of the drugs that attracted the attention of researchers at the beginning of the pandemic. It is an antiviral prodrug that inhibits viral replication by blocking RNA polymerase. Most of the preclinical studies of favipiravir have focused on its efficacy in the treatment of Ebola fever and influenza, but it demonstrated effectiveness against the SARS-CoV-2. An *in vitro* study by Wu et al. [1] revealed that favipiravir affects the virus in nearly 50% of cases. The results of the preclinical studies have enabled to consider favipiravir as an effective agent against COVID-19. Its overall safety profile was considered good, with respect to severe adverse events. However, concerns about the possibility of hyperuricemia, teratogenic effects, and prolongation of the *Q-T* interval after its intake have not been completely refuted [12].

The results of further studies of favipiravir were also controversial. It is no coincidence that the ClinicalTrial.gov website has registered approximately 60 randomized clinical trials evaluating the efficiency of favipiravir in patients with SARS-CoV-2 infection, as monotherapy or in combination with other agents [13]. In most of these trials, favipiravir was used at a dose of 600–800 mg twice a day, as in the treatment of severe pandemic influenza. They demonstrated heterogeneous results across different patient cohorts (inpatient vs. outpatient) and different primary endpoints (virologic vs. clinical). Some studies have shown that favipiravir can reduce the time to viral clearance in patients with mild-to-moderate COVID-19 or clinical improvement in the disease course. The drug is believed to be relatively safe for short-term use, but larger studies are required to confirm the findings [14].

In the Russian Federation, favipiravir (code in the anatomical–therapeutic–chemical classification J05AX27) was registered on May 29, 2020, as a drug intended for use in emergency situations. From September 17, 2020, the use of favipiravir preparations is allowed in outpatient practice. On June 3, 2020, favipiravir was included in version 7 of the interim recommendations of the Russian Ministry of Health for the diagnostics, prevention, and treatment of COVID-19 as an etiotropic therapy. In its country of origin (Japan), favipiravir is not approved for use in patients with COVID-19 [15].

The Russian study of favipiravir included 168 patients aged 18–60 years with confirmed COVID-19. They were randomized in a 2:1 ratio to the favipiravir group (1800 mg twice daily on day 1 and 800 mg twice daily from days 2–10) and the standard therapy group (umifenovir + intranasal interferon alpha-2b or hydroxychloroquine for up to 10 days). Patients also received the necessary concomitant symptomatic therapy. A total of 127 (75.5%) patients were included in the outpatient cohort, and 41 (24.5%) patients were enrolled in the inpatient cohort. Thus, the ratio of outpatients to hospitalized patients was 3:1. No separate comparison of the efficiency of favipiravir in groups was made, but in the favipiravir group, clinical improvement was registered 4 days earlier, and the frequency of clinical improvement

on day 7 was 1.5 times higher than that in the standard therapy group. Virus elimination on days 3 and 5 in the favipiravir group was significantly higher, as on day 3, it was noted in 71.4% and 57.1% of patients in the favipiravir and standard therapy groups, respectively. Patients tolerated favipiravir well, and most adverse events after its intake, such as asymptomatic hyperuricemia, transient increases in alanine and aspartate aminotransferase levels, and gastrointestinal disorders (diarrhea, nausea, and abdominal pain), were mild [16].

The safety of favipiravir in patients with COVID-19 requires further study. The entire range of the described adverse events inherent in this drug should receive attention. In female patients of childbearing age, it is necessary to conduct a pregnancy test before or after the therapy. In addition, strict adherence to effective contraception for 1 month after treatment completion is necessary. For men, barrier contraception is necessary for the same period. When using favipiravir, the levels of uric acid (especially in patients with gout) and transaminase activity should be controlled, and electrocardiography is required. The possibility of new, including serious, adverse effects, such as motor impairment and falls, should be considered [15]. A systematic review of the literature on the efficacy of favipiravir in the treatment of COVID-19 did not reveal its effect on such endpoints as the need for mechanical lung ventilation and mortality [17].

MOLNUPIRAVIR

Molnupiravir is a prodrug of the active antiviral analog of ribonucleoside β-D-N4-hydroxycytidine (NHC) and has activity against several RNA viruses, including the Middle East respiratory syndrome virus, and seasonal and pandemic influenza. After oral administration, molnupiravir is rapidly metabolized by esterases with NHC delivery to the systemic circulation. NHC is phosphorylated intracellularly to NHC triphosphate (NHC-TP), its pharmacologically active form. The incorporation of NHC-TP into the viral genome by the RNA polymerase of the virus during its replication leads to the accumulation of harmful mutations that exceed the threshold value, which prevents the virus from further replication [18].

Molnupiravir has demonstrated activity against SARS-CoV-2 *in vitro* and in experimental models. Volunteers tolerated it well when taken orally; thus, less than half of the participants reported side effects, which were mild in 93.3% of cases [19]. Data of the Molnupiravir Phase II clinical trial from the hospitalized group of patients with symptoms for 5 days (MOVE IN), 74% of whom had at least one risk factor for severe COVID-19, showed no side effects or adverse events requiring a dose reduction of the drug 800 mg twice daily. However, molnupiravir did not lead to a clinical effect in comparison with the placebo group [18].

The study of molnupiravir was continued in outpatients within phases II and III of the randomized placebo-controlled trial (MOVE OUT). All patients included in the study were laboratory confirmed to have mild or moderate COVID-19, and the onset of symptoms was noted 7 days before inclusion in the study protocol and randomization. The mean age of the patients was 49.2 (18–84) years, and 52.6% of them were men. The majority (75.2%) of the patients had an increased risk of severe disease, which were most often due to obesity (48.7%), age >60 years (23.5%), and diabetes mellitus (16.6%). The baseline demographic and clinical characteristics of the patients in both groups were comparable. The patients were randomly assigned in a 1:1:1:1 ratio to molnupiravir 200, 400, and 800 mg and placebo twice daily for 5 days and stratified by time since symptom onset and increased risk of severe COVID-19. The primary efficacy endpoint was the proportion of participants who were hospitalized and/or died within 29 days.

According to the study results, molnupiravir did not have a clinically significant dose-dependent effect on the incidence of adverse events. Seven patients in the molnupiravir group (3.1%) and 4 (5.4%) patients in the placebo group were hospitalized or died. Data analysis showed a lower rate of hospitalizations and/or lethal outcomes in the molnupiravir group than in the placebo group in individuals with increased risk of severe disease and patients who developed symptoms of COVID-19 5 days or earlier before randomization. This allowed the authors, based on the interim results of the study, to conclude that molnupiravir may be potentially reduce the number of hospitalizations and/or lethal outcomes in outpatients with COVID-19 [20].

Data from the phase III MOVE-OUT study of molnupiravir, which evaluated the safety and efficacy of molnupiravir in the outpatient treatment of adult patients with COVID-19, were published in February 2022 in *The New England Journal of Medicine* [21]. The study was conducted in 78 centers in 15 countries. Based on the positive results of the interim efficacy analysis, obtained on September 10, 2021, after 29 days of follow-up of 50% of 1550 patients (target set), an independent data monitoring committee recommended early termination of patient enrollment. The key inclusion criteria for randomization were laboratory confirmation of the presence of SARS-CoV-2 no more than 5 days before randomization, onset of signs or symptoms of the disease at the same time, and the presence of at least one of the risk factors for severe COVID-19, such as the following:

- Age >60 years;
- Cancer in the active stage;

- Chronic kidney disease;
- Chronic obstructive pulmonary disease;
- Obesity;
- Serious cardiovascular diseases (chronic heart failure, coronary heart disease, and cardiomyopathy);
- Diabetes mellitus.

The key exclusion criteria were as follows:

- Anticipated need for hospitalization for COVID-19 within the next 48 h;
- Dialysis or glomerular filtration rate <30 mL per minute per 1.73 m^2;
- Pregnancy;
- Unwillingness to use contraception during the intervention period and for at least 4 days after the completion of treatment (risk of the consequences of the teragenic effect of the drug);
- Severe neutropenia (absolute neutrophil count <500/mL);
- Platelet count <100,000/μL;
- Vaccination against SARS-CoV-2.

Standard treatment with antipyretic and anti-inflammatory drugs, glucocorticoids, or a combination thereof was allowed. The use of other etiotropic agents for the treatment of COVID-19, including any monoclonal antibodies and remdesivir, was prohibited until day 29 of the study. The patients were randomly distributed in a 1:1 ratio to the molnupiravir group (800 mg in four 200 mg capsules) and the placebo group (administered orally twice daily for 5 days). Randomization was divided into blocks depending on the time elapsed since the onset of the disease symptoms (<3 days or >3 days). The primary efficacy endpoint was the rate of hospital admissions for any cause (acute care for >24 h in a hospital or similar facility) or death within 29 days. The primary safety endpoint was the incidence of adverse events. The level of drug safety, including the proportion of patients with adverse events, was evaluated taking into account all patients who were randomized and received at least one dose of molnupiravir or placebo.

An analysis of the study results showed that 47.7% of the patients had signs or symptoms of COVID-19 no more than 3 days before randomization, and the disease moderate in 44.5% of the cases. The most common risk factors were obesity (73.7%), age >60 years (17.2%), and diabetes mellitus (15.9%). Antibodies to the SARS-CoV-2 nucleocapsid at baseline, indicating recent or previous infection (not vaccination), were reported in 19.8% of cases. In patients treated with molnupiravir, the risk of hospitalization or death within 29 days was lower, and its presence was detected in 6.8% of the patients in the molnupiravir group compared with 9.7% in the placebo group. There was one lethal outcome in the molnupiravir group (29-day all-cause mortality, 0.1%) and nine deaths in the placebo group (29-day all-cause mortality, 1.3%). The proportion of patients who experienced at least one adverse event was comparable in the molnupiravir (30.4%) and placebo (33%) groups. The most common (at least 2% of patients in any of the groups) adverse events were lung damage due to COVID-19 (6.3% in the molnupiravir group and 9.6% in the placebo group), diarrhea (2.3% and 3%, respectively), bacterial pneumonia (2% and 1.6%, respectively), and worsening of the COVID-19 course (an adverse event in 7.9% and 9.8%, respectively). The most common (at least 1% of patients in any of the groups) adverse events that were considered study-related were diarrhea (1.7% and 2.1%, respectively), nausea (1.4% and 0.7%, respectively), and dizziness (1% and 0.7%, respectively). The results of this study confirmed that molnupiravir can be considered a drug that, when prescribed promptly, is effective in preventing the severe course and mortality of COVID-19 in patients who are at risk because of age and comorbidities.

The study of molnupiravir within phases II and III of the clinical trial *Molnupiravir: Is It Time to Move In or Move Out* had some limitations, as none of the patients were vaccinated. Moreover, pregnant and immunocompromised individuals who may have more severe disease were excluded from the study. Nevertheless, the results became the basis for continuing the study of molnupiravir. In addition, both positive and negative test results of this drug are evidence of the urgent need for a comprehensive study of new effective and safe treatments for COVID-19 [22].

CONCLUSION

COVID-19 has become a serious challenge for clinicians and researchers, since etiotropic therapy, originally aimed at neutralizing SARS-CoV-2, was not available at the onset of the pandemic. The drugs presented herein (favipiravir and molnupiravir) were developed for the treatment of other viral diseases. Data on their efficacy and safety are controversial, and the study design does not always meet the criteria for good clinical practice. However, both drugs are included in the Russian guidelines for the treatment of COVID-19, which gives grounds for their use.

With the accumulation of data on the use of molnupiravir, which has passed all stages of clinical trials in other countries and will soon be available in Russia, more information about its efficacy and safety will become available. This drug was created primarily for outpatient use in patients with comorbidities that can induce severe COVID-19; thus, the benefits of its use should exceed the risk associated with the widespread introduction of a new pharmacological agent into clinical practice.

From the standpoint of the prospects for the use of favipiravir and molnupiravir, it is a matter of concern that both drugs are not yet included in the list of drugs recommended by the World Health Organization for the treatment of COVID-19, according to the latest updates of January 13, 2022 [9]. Version 15 of Russian interim guidelines [23] indicates a constant search for new means of etiotropic therapy, which lists several drugs analyzed at the final stages of clinical trials, and its results will be the subject of the second part of this article.

ADDITIONAL INFORMATION

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REFERENCES

1. Wu R, Wang L, Kuo HD, et al. An update on current therapeutic drugs treating COVID-19. *Curr Pharmacol Rep.* 2020:6(3):56–70. DOI: 10.1007/s40495-020-00216-7

2. Green N, Ott RD, Isaacs RJ, Fang H. Cell-based assays to identify inhibitors of viral disease. *Expert Opin Drug Discov.* 2008;3(6):671–676. DOI: 10.1517/17460441.3.6.671

3. Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) Is mediated by the viral polymerase and the proofreading exoribonuclease. *mBio.* 2018;9(2):e00221–18. DOI: 10.1128/mBio.00221-18

4. Vremennye metodicheskie rekomendatsii. Diagnostika, profilaktika i lechenie novoy koronavirusnoy infektsii (COVID-19). Versiya 7 (03.06.2020) [Internet]. Available from: http://edu.rosminzdrav.ru/fileadmin/user_upload/specialists/COVID-19/MR_COVID-19_v7.pdf. Accessed: March 3, 2022. (In Russ.)

5. Kandimalla R, John A, Abburi C, et al. Current status of multiple drug molecules, and vaccines: an update in SARS-CoV-2 Therapeutics. *Mol Neurobiol.* 2020;57(10):4106–4116. DOI: 10.1007/s12035-020-02022-0

6. VOZ prekrashchaet izyskaniya v gruppakh lecheniya COVID-19 gidroksikhlorokhinom i kombinatsiey lopinavira i ritonavira [Internet]. Available from: https://www.who.int/ru/news/item/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19. Accessed: March 3, 2022. (In Russ.)

7. Vremennye metodicheskie rekomendatsii. Diagnostika, profilaktika i lechenie novoi koronavirusnoy infektsii (COVID-19). Versiya 10 (08.02.2021) [Internet]. Available from: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/054/662/original/COVID-19_%28v.10%29.pdf. Accessed: March 3, 2022. (In Russ.)

8. 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: March 3, 2022.

9. Agarwal A, Rochwerg B, Lamontagne F, et al. A living WHO guideline on drugs for COVID-19. *BMJ.* 2020;370:m3379. DOI: 10.1136/bmj.m3379

10. Vremennye metodicheskie rekomendatsii. Diagnostika, profilaktika i lechenie novoy koronavirusnoy 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: March 3, 2022. (In Russ.)

11. Jalali N, Brustad HK, Frigessi A, et al. Increased household transmission and immune escape of the SARS-CoV-2 Omicron variant compared to the Delta variant: evidence from Norwegian contact tracing and vaccination data. *medRxiv.* DOI: 10.1101/2022.02.07.22270437

12. Kaur RJ, Charan J, Dutta S, et al. Favipiravir use in COVID-19: Analysis of suspected adverse drug events reported in the WHO database. *Infect Drug Resist.* 2020;13:4427–4438. DOI: 10.2147/IDR.S287934

13. Eloy P, Le Grand R, Malvy D, Guedj J. Combined treatment of molnupiravir and favipiravir against SARS-CoV-2 infection: One + zero equals two? *EBioMedicine.* 2021;74:103663. DOI: 10.1016/j.ebiom.2021.103595

14. Tejaswi P, Devashish K, Prasad RR. Pharmacological effects of Favipiravir on coronavirus: An update. *Biomed Pharmacol J.* 2021;14(2):1087–1095. DOI: 10.13005/bpj/2212

15. Kiselev YuYu, Matveev AV, Mirzaev KB, Sychev DA. Monitoring of safety using favipiravir: risk management of adverse drug reactions in clinical practice. *Good Clinical Practice.* 2020;(4S):115–119. (In Russ.). DOI: 10.37489/2588-0519-2020-S4-115-119

16. Ruzhentsova TA, Chukhlyaev PV, Khavkina DA, et al. Efficacy and safety of favipiravir in a complex therapy of mild to moderate COVID-19. *Infectious Diseases: News, Opinions, Training*. 2020;9(4):26–38. (In Russ.). DOI: 10.33029/2305- 3496-2020-9-4-26-38

17. Özlüşen B, Kozan Ş, Akcan RE, et al. Effectiveness of favipiravir in COVID-19: a live systematic review. *Eur J Clin Microbiol Infect Dis.* 2021;40(12):2575–2583. DOI: 10.1007/s10096-021-04307-1

18. Painter WP, Holman WL, Bush JA, et al. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2. *Antimicrob Agents Chemother.* 2021;65(5):e02428–20. DOI: 10.1128/AAC.02428-20

19. Arribas JR, Bhagani S, Lobo SM, et al. randomized trial of molnupiravir or placebo in patients hospitalized with COVID-19. *NEJM Evid.* 2021;1(2). DOI: 10.1056/EVIDoa2100044

20. Caraco Y, Crofoot GE, Moncada PA, et al. Phase 2/3 Trial of molnupiravir for treatment of Covid-19 in nonhospitalized adults. *NEJM Evid.* 2021;1(2). DOI: 10.1056/EVIDoa2100043

21. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. *N Engl J Med.* 2022;386(6):509–520. DOI: 10.1056/NEJMoa2116044

22. Castillo Almeida NE, Kalil AC. Molnupiravir: Is it time to move in or move out? *NEJM Evid.* 2021;1(2). DOI: 10.1056/EVIDe2100048
23. Vremennye metodicheskie rekomendatsii. Diagnostika, profilaktika i lechenie novoy koronavirusnoy infektsii (COVID-19). Versiya 15 (22.02.2022) [Internet]. Available from: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/059/392/original/COVID-19_V15.pdf. Accessed: March 3, 2022. (In Russ.)

СПИСОК ЛИТЕРАТУРЫ

1. Wu R., Wang L., Kuo H.D. et al. An update on current therapeutic drugs treating COVID-19 // Curr. Pharmacol. Rep. 2020. Vol. 6, No. 3. P. 56–70. DOI: 10.1007/s40495-020-00216-7
2. Green N., Ott R.D., Isaacs R.J., Fang H. Cell-based assays to identify inhibitors of viral disease // Expert Opin. Drug Discov. 2008. Vol. 3, No. 6. P. 671–676. DOI: 10.1517/17460441.3.6.671
3. Agostini M.L., Andres E.L., Sims A.C. et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734). Is mediated by the viral polymerase and the proofreading exoribonuclease // mBio. 2018. Vol. 9, No. 2. P. e00221–18. DOI: 10.1128/mBio.00221-18
4. Временные методические рекомендации. Диагностика, профилактика и лечение новой коронавирусной инфекции (COVID-19). Версия 7 (03.06.2020) [Электронный ресурс]. Режим доступа: http://edu.rosminzdrav.ru/fileadmin/user_upload/specialists/COVID-19/MR_COVID-19_v7.pdf. Дата обращения: 03.03.2022.
5. Kandimalla R., John A., Abburi C. et al. Current status of multiple drug molecules, and vaccines: an update in SARS-CoV-2 therapeutics // Mol. Neurobiol. 2020. Vol. 57, No. 10. P. 4106–4116. DOI: 10.1007/s12035-020-02022-0
6. ВОЗ прекращает изыскания в группах лечения COVID-19 гидроксихлорохином и комбинацией лопинавира и ритонавира [Электронный ресурс]. Режим доступа: https://www.who.int/ru/news/item/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19. Дата обращения: 03.03.2022.
7. Временные методические рекомендации. Диагностика, профилактика и лечение новой коронавирусной инфекции (COVID-19). Версия 10 (08.02.2021) [Электронный ресурс]. Режим доступа: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/054/662/original/COVID-19_%28v.10%29.pdf. Дата обращения: 03.03.2022.
8. 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: 03.03.2022.
9. Agarwal A., Rochwerg B., Lamontagne F. et al. A living WHO guideline on drugs for COVID-19 // BMJ. 2020;370:m3379. DOI: 10.1136/bmj.m3379
10. 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: 03.03.2022.
11. Jalali N., Brustad H.K., Frigessi A. et al. Increased household transmission and immune escape of the SARS-CoV-2 Omicron variant compared to the Delta variant: evidence from Norwegian contact tracing and vaccination data // medRxiv. DOI: 10.1101/2022.02.07.22270437
12. Kaur R.J., Charan J., Dutta S. et al. Favipiravir use in COVID-19: Analysis of suspected adverse drug events reported in the WHO database // Infect. Drug Resist. 2020. Vol. 13. P. 4427–4438. DOI: 10.2147/IDR.S287934
13. Eloy P., Le Grand R., Malvy D., Guedj J. Combined treatment of molnupiravir and favipiravir against SARS-CoV-2 infection: One + zero equals two? // EBioMedicine. 2021;74:103663. DOI: 10.1016/j.ebiom.2021.103595
14. Tejaswi P., Devashish K., Prasad R.R. Pharmacological effects of Favipiravir on coronavirus: an update // Biomed. Pharmacol. J. 2021;14(2):1087–1095. DOI: 10.13005/bpj/2212
15. Киселёв Ю.Ю., Матвеев А.В., Мирзаев К.Б., Сычёв Д.А. Мониторинг безопасности применения фавипиравира: управление рисками развития нежелательных лекарственных реакций в клинической практике // Качественная клиническая практика. 2020. № S4. С.115–119. DOI: 10.37489/2588-0519-2020-S4-115-119
16. Руженцова Т.А., Чухляев П.В., Хавкина Д.А. и др. Эффективность и безопасность применения фавипиравира в комплексной терапии COVID-19 легкого и среднетяжелого течения // Инфекционные болезни: новости, мнения, обучение. 2020. Т. 9, № 4. С. 26–38. DOI: 10.33029/2305- 3496-2020-9-4-26-38
17. Özlüşen B., Kozan Ş., Akcan R.E. et al. Effectiveness of favipiravir in COVID-19: a live systematic review // Eur. J. Clin. Microbiol. Infect. Dis. 2021. Vol. 40, No. 12. P. 2575–2583. DOI: 10.1007/s10096-021-04307-1
18. Painter W.P., Holman W.L., Bush J.A. et al. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2 // Antimicrob. Agents Chemother. 2021. Vol. 65, No. 5. P. e02428–20. DOI: 10.1128/AAC.02428-20
19. Arribas J.R., Bhagani S., Lobo S.M. et al. randomized trial of molnupiravir or placebo in patients hospitalized with Covid-19 // NEJM Evid. 2021. Vol. 1, No. 2. DOI: 10.1056/EVIDoa2100044
20. Caraco Y., Crofoot G.E., Moncada P.A. et al. Phase 2/3 trial of molnupiravir for treatment of Covid-19 in nonhospitalized adults // NEJM Evid. 2021. Vol. 1, No. 2. DOI: 10.1056/EVIDoa2100043
21. Jayk Bernal A., Gomes da Silva M.M., Musungaie D.B. et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients // N. Engl. J. Med. 2022. Vol. 386, No. 6. P. 509–520. DOI: 10.1056/NEJMoa2116044
22. Castillo Almeida N.E., Kalil A.C. Molnupiravir: Is it time to move in or move out? // NEJM Evid. 2021. Vol. 1, No. 2. DOI: 10.1056/EVIDe2100048
23. Временные методические рекомендации. Диагностика, профилактика и лечение новой коронавирусной инфекции (COVID-19). Версия 15 (22.02.2022) [Электронный ресурс]. Режим доступа: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/059/392/original/COVID-19_V15.pdf. Дата обращения: 03.03.2022.

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