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CURRENT ASPECTS OF ETIOTROPIC COVID-19 THERAPY

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Since the beginning of the pandemic, repeated attempts have been made to develop etiotropic therapy for a novel coronavirus infection. Hydroxychloroquine, lopinavir/ritonavir, etc. derivatives were used as antiviral agents, however, they demonstrated a low efficiency and an insufficient safety. In this connection, other groups of drugs with a more effective and safe pharmacological profile are currently being actively used.
The aim of the study was to analyze the literature references on the efficacy and safety of antiviral drugs for the COVID-19 treatment.
Materials and methods. When searching for the materials for the review article writing, such abstract databases as PubMed, Google Scholar, e-Library were used. The search was carried out on publications for the period from January 2020 to September 2022. The key queries were: COVID-19, etiotropic therapy; immunological drugs; antiviral drugs; interferons.
Results. Currently, there are various degrees of effective etiotropic drugs for the treatment of COVID-19 patients. The review has considered a few groups of drugs that are of interest from the point of view of etiotropic therapy: immunological drugs (anticovid plasma, the drugs based on antiviral antibodies, the drugs of recombinant interferons-α2 and -β1, as well as interferon inducers, i.e., the drugs based on double-stranded RNA sodium salt, and others); drugs that block the penetration of the virus into the cell (umifenovir); the drugs that disrupt the process of the viral replication (favipiravir, remdesivir, molnupiravir, nirmatrelvir/ritonavir).
Conclusion. Synthetic antivirals, in particular favipiravir, molnupiravir, remdesivir, and nirmatrelvir/ritonavir, have the largest evidence base for their efficacy and safety. The search for new effective and safe etiotropic drugs for the treatment of COVID-19, as well as the collection and analysis of post-registration data on the drugs already used in clinical practice, continues.
Keywords: COVID-19; interferons; molnupiravir; favipiravir; nirmatrelvir/ritonavir; etiotropic therapy
Abbreviations: IFN – interferon; II – interferon inducers; IVIG – intravenous immunoglobulin; dsRNA – double-stranded ribonucleic acid; siRNA – small interfering RNA; ARDS – acute respiratory distress syndrome; OR – odds ratio; CI – confidence interval; RR – risk ratio; AE - adverse events; ALV – artificial lung ventilation.

АКТУАЛЬНЫЕ АСПЕКТЫ ЭТИОТРОПНОЙ ТЕРАПИИ COVID-19

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С начала пандемии предпринимались неоднократные попытки разработки этиотропной терапии новой коронавирусной инфекции. В качестве противовирусных средств использовались производные гидроксихлорохина, лопинавир/ритонавир и др., однако они продемонстрировали невысокую эффективность и недостаточную безопасность. В связи с чем, в настоящее время активно применяются другие группы препаратов, обладающих более эффективным и безопасным фармакологическим профилем.

Цель. Анализ литературных данных по эффективности и безопасности противовирусных препаратов для лечения COVID-19.

Материалы и методы. При поиске материала для написания обзорной статьи использовали такие реферативные базы данных, как PubMed, Google Scholar, e-Library. Поиск осуществлялся по публикациям за период с января 2020 по сентябрь 2022 гг. Ключевые запросы: COVID-19, этиотропная терапия/etiotropic therapy; иммунологические препараты/immunologic drugs; противовирусные препараты/antiviral drugs; интерфероны/interferons.

Результаты. В настоящее время имеются в разной степени эффективные этиотропные препараты для лечения пациентов с COVID-19. В обзоре рассмотрены несколько групп лекарственных препаратов, представляющих интерес с точки зрения этиотропной терапии: иммунологические препараты (антиковидная плазма, препараты на основе противовирусных антител, препараты рекомбинантных интерферонов-α2 и -β1, а также индукторы интерферона, например, препараты на основе РНК двуспиральной натриевой соли и др.); препараты, блокирующие проникновение вируса в клетку (умифеновир); препараты, нарушающие процесс репликации вируса (фавипиравир, ремдесивир, молнупиравир, нирматрелвир/ритонавир).

Заключение. Наиболее объемную доказательную базу данных по эффективности и безопасности имеют синтетические противовирусные средства, в частности фавипиравир, молнупиравир, ремдесивир и нирматрелвир/ритонавир. Поиск новых эффективных и безопасных этиотропных препаратов для лечения COVID-19 продолжается, также как сбор и анализ пострегистрационных данных об уже применяющихся в клинической практике средствах.

Ключевые слова: COVID-19; интерфероны; молнупиравир; фавипиравир; нирматрелвир/ритонавир; этиотропная терапия

Список сокращений: ИНФ – интерферон; ИИ – индукторы интерферонов; ВВИГ – внутривенный иммуноглобулин; дсРНК – двуспиральная рибонуклеиновая кислота; миРНК – малая интерферирующая рибонуклеиновая кислота; ОРДС – острый респираторный дистресс-синдром; ОШ – отношение шансов; ДИ – доверительный интервал; ОР – отношение рисков; НЯ – нежелательные явления; ИВЛ – искусственная вентиляция легких.

INTRODUCTION

The novel coronavirus infection has challenged all of humanity, showing the global vulnerability of the society to infectious diseases. The main target of SARS-CoV-2 is the respiratory system, however, in addition to the fatal pulmonary complications of COVID-19, the patients have a variety of dangerous extrapulmonary manifestations, including thrombotic complications, an acute kidney injury, and "acute" cardiovascular disorders [1, 2]. The prognosis for COVID-19 is determined by a combination of individual risk factors (age, comorbidities, healthcare organizations).

In the retrospective study by Magleby R. et al., comprising 678 hospitalized COVID-19 patients, it was demonstrated that an independent risk factor for mortality (odds ratio (OR)=6.05; p <0.001) and the crossover to the artificial lung ventilation (ALV) (OR=2.73; p <0.001) is a high viral load [3]. An early initiation of the antiviral therapy contributes to an effective reduction in the viral load, reduces the risk of the disease progression and improves the prognosis [4]. In this regard, in the early phase of the disease, when the maximum replication rate of SARS-CoV-2 is notified, the antiviral therapy is of primary importance, while in later periods, the hyperinflammatory syndrome and coagulopathy take the leading places in the pathogenesis of the disease, respectively, the role of anti-inflammatory drugs (glucocorticosteroids), immunomodulating agents, anticoagulants and their combinations, increases [5]. However, it should be notified that the antiviral therapy remains a significant even at the late stages of the disease, due to the long-term (from 17 to 27 days) viral shedding in patients, especially those with a severe infection [6].

Since the beginning of the pandemic, repeated attempts have been made to develop etiotropic therapy for a novel coronavirus infection. Hydroxychloroquine, lopinavir/ritonavir, etc. derivatives were used as antiviral agents, however, they demonstrated a low efficiency and an insufficient safety [7–10]. In this connection, other groups of drugs with a more effective and safe pharmacological profile are currently being actively used.

THE AIM of the study was to analyze the literature references on the efficacy and safety of antiviral drugs for the COVID-19 treatment.

MATERIALS AND METHODS

When searching for the materials for the review article writing, such abstract databases as PubMed, Google Scholar, e-Library were used. The search was carried out on publications for the period from Jan 2020 to Sep 2022. The key queries were: COVID-19, etiotropic therapy; immunological drugs; antiviral drugs; interferons. The data from both clinical and *in vitro* trials, were considered as references.

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RESULTS AND DISCUSSION

At the moment, the following groups of etiotropic drugs for the treatment of COVID-19 can be distinguished (Table 1):

1) immunological drugs (anticovid plasma, preparations based on antiviral antibodies, preparations of recombinant interferons-α2 and -β1, as well as interferon inducers, i.e., the drugs based on double-stranded RNA sodium salt, and others);

2) drugs that block the penetration of the virus into the cell (umifenovir);

3) drugs that disrupt the process of the viral replication (favipiravir, remdesivir, molnupiravir, nirmatrelvir/ritonavir).

1. Immunological drugs

1.1. Anticovid plasma

Plasma from the patients who have been cured of the COVID-19 infection, is a source of antiviral antibodies and is considered as a treatment option backed by a significant historical experience, but still promising in the context of SARS-CoV-2. In addition to the antiviral (virus-neutralizing) effect, plasma reduces an antibody-dependent cellular cytotoxicity, a complement activation, and phagocytosis [11]. Theoretically, the administration of convalescent plasma at an early stage of the disease is more effective [12], since the peak of viremia is observed in the first week of the infection, and the native primary immune response usually develops on the 10–14th days [13]. In addition to direct antiviral effects, plasma components can also restore the activity of the hemostasis system [14].

Against the background of the conventional therapy and in the controlled study, in patients with severe COVID-19, in the description of individual series of plasma clinical cases, positive results were obtained in 76–90% [15–17]. A donor selection according to the titers or the activity of neutralizing antibodies can further increase the efficacy of anticovid plasma [18]. Clinical and biochemical predictors of the plasma efficacy are lymphopenia, elevated levels of procalcitonin, ferritin, D-dimer and C-reactive protein. It is believed that the preference should be given to the patients who are in a non-critical condition, at the early stage of the disease [19]. A potential danger lies in the intensification of the disease in the presence of certain antibodies – an antibody-dependent increase in the penetration of coronavirus [20]. An analysis of more than 5 000 patients with a severe or life-threatening COVID-19 infection treated with anticovid plasma, showed that serious adverse events (AEs) occurred in <1% of patients in the first 4 h after the infusion [21].

1.2. Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) can inhibit the complement cascade activation of pro-inflammatory cytokines, differentiation and activation of dendritic cells, as well as the activation of neutrophils and the formation of neutrophil extracellular traps [22]. Considering that these mechanisms can play an important role in the pathogenesis of a novel coronavirus infection, IVIG is one of the options for treating COVID-19 [23]. In a multicenter, double-blind, placebo-controlled (Phase 3) study of 146 patients (69 of whom 69 had received IVIG, 77 – placebo) with an acute respiratory distress syndrome (ARDS) due to COVID-19, the use of IVIG did not improve clinical outcomes (on day 28) and was associated with a slight increase in the incidence of thromboembolic complications [24].

1.3. Interferons

Based on the pathogenetic mechanisms of infection caused by SARS-CoV-2, a possible drug target is the interferon (IFN) system. The SARS-CoV-2 virus can inhibit the induction of type I and type III IFNs [25]. In the study by Contoli M. et al., the hospitalized COVID-19 patients with a respiratory failure had 3.8 times lower levels of IFN-α compared to the controls. Herewith, the improvement in the patients' condition was accompanied by an increase in the blood level of the same IFN-α [26]. In addition, the patients with congenital defects in the type I IFN system (with the presence of autoantibodies) have a predisposition to a severe COVID-19 [27]. In the treatment of COVID-19, the antiviral effect of IFN-α2b is determined by the time of the therapy initiation [28].

1.4. Double-stranded RNA sodium salt

The data accumulated by now, show that interferon inducers (IIs) of double-stranded ribonucleic acid (dsRNA), sodium ribonucleonate, being a multiclonal stimulator, induces the synthesis of IFN by several cell populations (cells of the mononuclear phagocytic system, granulocytes, neutrophils, endothelial cells and fibroblasts), characterized by a high (specific) activity and safety.

By activating a number of Toll-like receptors, dsRNA stimulates the synthesis of endogenous IFNs (α, β, γ), which block the ability of the cells to support a viral reproduction by both activating the synthesis of proteins that inhibit the production of viral copies in affected cells and, possibly, damaging the genetic virus material when interacting with the host cell (similar to siRNA effects). Subsequently, both NK cells and mechanisms of adaptive immunity are activated.

In the Russian Federation, a medicinal product based on the dsRNA sodium salt (Radamin® Viro

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LS-000381[1] dated 03 Aug 2010, date of renewal 27 Dec 2021), is registered. When administrated into the body, dsRNA stimulates the formation of endogenous IFN I (IFN-α, IFN-β) and IFN II (IFN-γ) types, which are the most important cytokines of the immune response, induce differentiation of myeloid cells, stimulate phagocytosis of neutrophils and macrophages, activate NK cells, enhance the Th1-type T-helper response, thus triggering the innate and adaptive immune response. The antiviral effect of the drug is associated with the activation of the proteins synthesis inhibiting the production of viral copies in the affected cells [29].

DsRNA belongs to the "early type" of interferon inducers, while the production of IFN occurs within 2-6 hours after the administration of the drug with a return to the background values within 2 days. The drug inhibits the reproduction of viruses and various microorganisms (including chlamydia) at the cellular level, prevents the development of the infectious process by activating the body's nonspecific resistance, optimizing inflammatory reactions. Due to its mechanism of action, the drug provides a high protection of the body at already early stages of viral or bacterial infections, has a pronounced anti-inflammatory effect, and also indirectly stimulates reparative and regenerative processes in the body, has antiviral, antibacterial and immunostimulating effects, and also increases the body's resistance to infections [29].

As an II, dsRNA itself has been known for more than 10 years. However, a new technology for the production of dsRNA sodium salt has made it possible to obtain a highly purified biological product, which significantly increases the safety of the drug and opens up broad prospects for its use in clinical practice [29].

2. Drugs that block virus penetration into cell

2.1. Umifenovir

Since the start of the pandemic, umifenovir has been one of the first widely used synthetic antiviral drugs in our country. It is a broad-spectrum antiviral drug that blocks the entry of viruses into host cells by inhibiting the fusion of the lipid envelope of the virus with the cell membrane. Initially, umifenovir was developed for the prevention of the influenza treatment [30]. It has demonstrated an activity against SARS-CoV-2 *in vitro* [31]. In the meta-analysis assessing the efficacy and safety of umifenovir in COVID-19, it was found out that the use of the drug was associated with a higher incidence of negative PCR results on the 14th day of illness (OR=1.27; 95% CI=1.04–1.55) compared with the control group, however, was not associated with a reduction in the risk of the COVID-19 progression, a clinical improvement, and a duration reduction in hospital stay [32].

3. Drugs that disrupt viral replication process

Recently, the drugs able of inhibiting RNA-dependent RNA polymerase of direct action, which is an important enzyme of RNA-containing viruses, have been of primary importance in the development of the antiviral therapy strategy for COVID-19 and ensuring their replication [33].

3.1. Favipiravir

Favipiravir, synthesized and patented by Japanese scientists Y. Furuta and H. Egawa in the late 1990s, is a broad-spectrum antiviral drug proposed for the treatment of severe viral infections, including influenza A, B and C, as well as Ebola. [34]. In 2014, this drug was approved in Japan for the treatment of the infection caused by a pandemic variant of the influenza virus or when other drugs had failed. The subsequent studies have shown that favipiravir is highly active against a large group of RNA-containing viruses, such as influenza viruses, bunya-, arena-, flavi-, picoranaviruses, etc. [35]. In an experimental study by Yamada K. et al., favipiravir has been shown to be effective for a post-exposure prophylaxis of rabies and may be a suitable alternative to immunoglobulin [36]. Favipiravir has shown a good inhibitory activity *in vitro* against SARS-CoV-2, but relatively high doses of the drug are required to obtain effective inhibitory concentrations and provide an antiviral activity [35].

Favipiravir is a prodrug, its active form is ribofuranosyl triphosphate. As a nucleoside analogue, it inhibits the SARS-CoV-2 RNA-dependent RNA polymerase complex by binding to its catalytic domain and preventing the incorporation of nucleotides for a viral RNA replication, which leads to an increase in the mutation frequency and a possible lethal mutagenesis. Also important note that RNA-dependent RNA polymerase is absent in human cells, so the drug is active only contrary virus [37, 38].

The Ministry of Health of the Russian Federation has issued an accelerated permission to use favipiravir preparations for the treatment of COVID-19 [37]. Similar approvals have been obtained in China, India and other countries. In phase II/III of the clinical study in sixty patients, favipiravir therapy was well tolerated and safe, resulting in viral clearance in 62.5% of COVID-19 patients after four days. On the fifth day, twice as many patients treated with favipiravir, received a negative PCR result for SARS-CoV-2 compared with the patients in the control group ($p < 0.05$) [39].

A lot of clinical trials and observatory studies which reported on the effectiveness and safety of

[1] Russian State Register of Medicines. Instructions for Radamin® Viro. Available from: https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=27d5a81d-b2e9-49d2-a9eb-1f1c9eacbaa4

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Favipiravir in the treatment of COVID-19 patients, have been conducted [38–44]. Alamer A. et al. assessed the effectiveness of Favipiravir in the treatment of COVID-19 (n=457). It has been established that the average time from the onset of the disease to discharge was 10 days (95% CI = 9–10) in the group of patients receiving favipiravir (n=234), versus 15 days (95% CI=14–16) in the comparison group, receiving supporting therapy (n=223) [38]. In the prospective open multicenter clinical study, including 240 COVID-19 patients (120 patients received Favipiravir, 120 – Umifenovir), in the group of favipiravir patients, there was a faster decrease in the temperature and a decrease in the cough severity [40].

According to the results of the open randomized multicenter comparative study (N = 206), the use of favipiravir for the COVID-19 treatment contributed to a more rapid improvement of the condition (6-8 days) compared with the use of the standard therapy (7–12 days), also demonstrating a favorable security profile. According to the PCR, the Elimation of SARS-COV-2 to the 10th day of therapy was recorded in 98% of the favipiravir patients, and in 80% in the control group (p=0.00007). AEs were observed in 24.04% of the patients of the main group and in 27.45% – the control group [41].

In a number of meta-analyses that summarize the data of clinical studies, the benefits of adding favipiravir to the standard therapy, were confirmed [43, 44]. In the hospitalized patients, Favipiravir, compared with the control group that were receiving only the standard therapy, contributed to a faster elimination of the virus – an average of 5 days (OR=1.60; p=0.02), an earlier temperature decrease – an average of 3 by an average of the 3–4th day (OR=1.99; p <0.01), an improvement in the radiological picture in the lungs (OR=1.33; p <0.01) and an earlier discharge from the hospital (OR=1.19; p <0.01). As for the AEs, the Favipiravir group recorded a higher frequency of hyperuricemia (OR=9.42; p <0.01), increased levels of alanineine-veransferase (OR=1.35; p <0.01), but a lower frequency of nausea (OR=0.42; p <0.01) and vomiting (OR=0.19; p=0.02). The authors arrived at the conclusion that the addition of Favipiravir to the standard therapy is beneficial to the hospitalized COVID-19 patients. At the same time, it has been notified that pregnant women and patients with hyperuricemia in an anamnesis should avoid the use of phavipiral [43].

Favipiravir for *per os* administration has proved to be quite effective and safe for the treatment of a novel coronavirus infection in both mild and moderate courses and has occupied its niche in the outpatient practice. However, in complicated cases, the parenteral therapy has advantages over the oral route of the drug delivery. This therapy can be used in the situations where the patient is in a serious condition or unconscious, has swallowing difficulties or conditions that prevent swallowing. It may also be important in patients with gastrointestinal COVID-19 symptoms, in patients with antibiotic-associated diarrhea (uncontrolled use of antibiotics combinations on an outpatient basis), the exacerbation of chronic gastrointestinal diseases and pseudomembranous colitis, and other situations where the p. o. administration is difficult). The intravenous route of the drug administration is used for a quick and pronounced result, since it immediately enters the bloodstream, its quickly provides maximum bioavailability and the pharmacokinetics are generally more predictable – there is no interaction with food and digestive enzymes [42]. In view of this, in 2021 in the RF was developed and registered a new dosage form of favipiravir for the parenteral administration – Areplivir® (RU LP-007598 dated 18 May 2022), was registered. In the clinical centers of Moscow, Smolensk, Yaroslavl, St. Petersburg, Saransk and Ryazan, an open randomized multicenter comparative study of favipiravir for the parenteral administration (n=209) was conducted in the hospitalized patients aged 18–80 years with moderate form of the coronavirus infection. Based on the results of the study, the data were obtained confirming a high efficacy and safety of the parenteral form of favipiravir for the treatment of COVID-19. In the main group, by the 10th day of therapy, an improvement in the clinical status by 2 or more points on the World Health Organization (WHO) scale was observed in 56.86% of patients, which corresponds to mild symptoms or the complete absence of signs of the disease, and in the control group (the patients receiving the standard therapy) – in 28.04% (p <0.0001). In the group of favipiravir patients, the clinical status improved faster (median=5 days) than in the control group (7 days). On days 5 and 14 of the treatment (visits 2 and 4), a more pronounced improvement in the clinical status was recorded in the main group, in contrast to the patients in the comparison group [42].

A faster and more enhanced favipiravir action for the parenteral use is aimed at increasing the effectiveness of therapy and preventing the development of an extremely severe COVID-19 course, getting to the resuscitation and intensive care unit and death [42, 45].

3.2. Remdesivir

One of the first drugs in the group of RNA-dependent RNA polymerase inhibitors was remdesivir, originally developed for the treatment of the infection caused by the Ebola virus. It is a prodrug that inhibits the reproduction of a wide range of viruses, including filo-, paramyxo-, pneumo- and ortho-coronaviruses (SARS-

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CoV and a Middle East respiratory syndrome coronavirus [MERSCoV]) [46–48]. This drug is administered parenterally, which makes it difficult to be used on an outpatient basis[2]. Remdesivir in high doses inhibits the enzyme RNA-dependent RNA polymerase of the virus, causing a delayed termination of the RNA chain without affecting the activity of human polymerases[3] [49, 50].

The National Institute of Allergy and Infectious Diseases (NIAID) in the United States has initiated a placebo-controlled, double-blind, randomized Phase III trial to evaluate the efficacy and safety of remdesivir versus placebo (NCT04280705). This study included 1062 hospitalized patients with COVID-19 and signs of a lower respiratory tract infection (541 patients in the remdesivir group, 521 patients in the placebo group). In the patients treated with remdesivir, the median recovery time was 10 days (95% CI=9-11) compared with 15 days (95% CI=13-18) in the placebo group (OR=1.29; 95% CI = 1.12–1.49; p <0.001). Serious AEs were reported in 131 of 532 patients treated with remdesivir (24.6%) and in 163 of 516 patients treated with placebo (31.6%). The authors concluded that remdesivir is superior to placebo in terms of its effect on the duration of the disease and the severity of clinical symptoms [46].

In patients with moderate COVID-19 who received a 10-day course of remdesivir, there was no statistically significant difference in the clinical status compared to the standard therapy by day 11 of treatment. The patients treated with a 5-day remdesivir course, had a statistically significant difference in clinical status compared to the standard therapy (OR=1.65; 95% CI =1.09–2.48; p=0.02), but this difference, according to the researchers, had no clinical significance [50]. In some other randomized trials, it was not possible to obtain any convincing evidence of the remdesivir effectiveness, either.

Despite the mixed trial results, the FDA has approved remdesivir for the use in hospitalized adult patients with severe COVID-19. Subsequently, the range of indications was expanded and remdesivir was also recommended for the treatment of COVID-19 children aged ≥28 days and weighing ≥3 kg[4]. The data from a number of other clinical studies have also been published in support of the final approval [51–56]. In the double-blind, placebo-controlled study (n=562) of unvaccinated outpatients aged ≥12 years (with one or more risk factors for severe COVID-19), the risk of hospitalization was 87% lower in the remdesivir group (n=279) compared with placebo (n=283) (95% CI=0.03-0.59) [51]. In the study by Goldman D.L. et al., in 77 children with severe COVID-19, the remdesivir therapy was characterized by a favorable safety profile with a high clinical recovery rate [52].

To date, many additional randomized controlled trials and meta-analyses have been obtained, though their conclusions are still conflicting. Among all these works, the most authoritative is the independent WHO Solidarity study, which, according to the results of the interim analysis, did not reveal a significant effect of remdesivir (as well as other antiviral drugs) on mortality rates in hospitalized COVID-19 patients [54]. For this reason, the WHO did not initially recommend the use of remdesivir in these patients. However, the continuation of the study found out that remdesivir had no effect on the survival of ventilated COVID-19 patients, while it slightly reduced the risk of death (up to 14.6% compared to 16.3% in the control group) or the crossover to the artificial lung ventilation (ALV) (14.1% versus 15.7% in the control group) of the hospitalized patients [54]. Based on these data, the WHO has revised its conclusions regarding the use of remdesivir, and now remdesivir is recommended for the treatment of mild to moderate COVID-19, where there is a high risk of hospitalization[5]. Singh S. et al. summarized the data from 4 studies involving 7,324 patients. No reduction in mortality was observed with remdesivir compared with controls (OR=0.92; 95% CI=0.79–1.07; p=0.30). The authors concluded that, given the lack of a significant effect on mortality and a high cost of the drug, its use in COVID-19 is not appropriate, especially in low-income countries [54].

3.3. Molnupiravir

Molnupiravir has become another innovative drug that has not been previously used in clinical practice and received an accelerated approval during the COVID-19 pandemic. It is a prodrug, an analog of N-hydroxycytidine, which is phosphorylated to form N-hydroxycytidine triphosphate and is integrated into viral RNA with the help of RNA polymerase, leading to the accumulation of mutations in the virus genome and, as a result, inhibiting a replication [57]. Molnupiravir is active against RNA-containing viruses, including SARS-CoV-2, which has been shown in experiments *in vitro* and *in vivo* [58]. The results of phase I/II/III clinical trials confirmed the efficacy and safety of molnupiravir in COVID-19 [59, 60].

During conducting a phase I clinical study on healthy volunteers (n=130), the data on a good tolerability of the

[2] Cohen P, Gebo K. COVID-19: Outpatient evaluation and management of acute illness in adults. UpToDate. Literature review current through: Jun 2022.

[3] Coronavirus (COVID-19) update: FDA approves first COVID-19 treatment for young children. Available from: https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-approves-first-covid-19-treatment-young-children.

[4] Ibid.

[5] Remdesivir for COVID-19. Available from: https://apps.who.int/iris/bitstream/handle/10665 /359753/WHO-2019-nCoV-Therapeutics-Remdesivir-Poster-A-2022.1-eng.pdf

drug were obtained. 35.4% and 43.8% (control group) of patients experienced mild side effects with a single dose, 42.9% and 50.0% (control group) – with multiple increasing doses, respectively [59]. By PCR, in a phase IIa clinical trial (n=202), SARS-CoV-2 virus clearance was shorter in the study group compared with placebo (median = 14 days for molnupiravir and 27 days for placebo; p=0,01)[6].

The Phase III, double-blind, randomized, placebo-controlled MOVe-OUT trial included 1 433 non-hospitalized adult patients with mild to moderate COVID-19 (the most common SARS-CoV-2 variants were delta (58.1%), mu (20.5%), gamma (10.7%) and the presence of at least one risk factor for a severe novel coronavirus infection (716 participants received molnupiravir, 717 – placebo). Patients from 15 Russian centers also participated in the MOVe-OUT study. The risk of hospitalization or death was lower in the molnupiravir group (6.8%) compared with placebo (9.7%) (95% CI=5.9−0.1%). The frequency of the AEs registration (including viral pneumonia) in the group of patients receiving molnupiravir was comparable to that in the placebo group (30.4% and 33.0%, respectively). The most common side effects were: diarrhea (1, 7% and 2.1%), nausea (1.4% and 0.7%) and dizziness (1.0% and 0.7%) [60].

Due to the increase in the incidence of COVID-19 and the need to introduce effective drugs for its treatment into clinical practice, the Russian Federation has also developed and registered the drug molnupiravir (Esperavir®) in the oral dosage form capsules (LP-007856 dated 18 May 2022)[7]. According to the results of the clinical study involving 240 outpatients with mild to moderate COVID-19 from 12 Russian centers, the use of molnupiravir for 5 days at the dose of 800 mg 2 times a day led to a 4-fold reduction in the risk of worsening the disease course to the 2nd study week compared with the standard therapy (p=0.0149). It should be notified that about 70% of the patients who participated in the study had concomitant diseases (mainly obesity of degree 2 and above, as well as arterial hypertension).

An important indicator for predicting a COVID-19 course is the virus elimination rate. In 71.67% of patients treated with molnupiravir, SARS-CoV-2 RNA in a swab from the nasopharynx and / or oropharynx was not detected already 6–7 days after the therapy start. In 19% of patients in the molnupiravir group, a complete clinical recovery had been achieved by days 6-7. In the standard therapy group, only 6% of patients (p=0.0039) had been cured by this point.

The treatment of COVID-19 with molnupiravir also led to a significant decrease compared to the standard therapy in the frequency and severity of the disease symptoms, such as cough, changes in osphresis and taste sensitivity over the latest 24 hours after 6–7 days from the therapy start. The data obtained indicate significant advantages of molnupiravir compared to the standard therapy in terms of the dynamics of the COVID-19 symptoms disappearance, the viral load reduction, the improvement in the condition of patients and their clinical status. Therapy with molnupiravir was well tolerated, most of the AEs were of a mild severity, there were no cases of therapy discontinuation or changes in the dose of the study drug due to the development of AEs [61].

Molnupiravir is contraindicated during pregnancy and lactation, and is also prohibited in patients under 18 years [57].

3.4. Nirmatrelvir/ritonavir

The data on the antiviral efficacy of the nirmatrelvir and ritonavir combination in the treatment of COVID-19 are being accumulated. The combination with a commercial product name Paxlovid, was developed by Pfizer and approved by the FDA for an emergency use in mild to moderate COVID-19 in adults and children over 12 years of age at high risk of developing a severe disease. This drug is included in the WHO recommendations for the treatment of COVID-19 [62, 63]. Nirmatrelvir is an inhibitor of the 3-chymotrypsin-like enzyme of SARS-CoV-2 cysteine protease (M^{pro}), which is involved in the viral replication. It has a high antiviral activity against different types of SARS-CoV-2, including alpha (B.1.1.7), beta (B.1.351), gamma (P.1), delta (B.1.617.2) and omicron (B.1.1.529) variants [64]. Ritonavir, an inhibitor of cytochrome P450 3A4, acts as a pharmacokinetic booster, slowing down the nirmatrelvir metabolism of [62, 63]. In December 2021, the combination medicine nirmatrelvir/ritonavir was first approved in the UK for the treatment of COVID-19 in adults who did not require supplemental oxygen and are at the increased risk of progression to severe COVID-19. In January 2022, this drug was approved for the same indications in the European Union, then in the United States, as well as in several other countries.

To date, two randomized trials have shown that the use of nirmatrelvir/ritonavir in outpatients with mild to moderate COVID-19 for 5 days leads to a reduction in hospitalization and mortality [62, 64]. The double-blind, randomized, placebo-controlled EPIC-HR Phase

[6] US Food and Drug Administration. Fact sheet for healthcare providers: emergency authorization for Paxlovid. 2022. Available from: https://www.fda.gov/media/155050/download. Accessed 30 April 2022.

[7] Russian State Register of Medicines. Instructions for molnupiravir (Esperavir®). Available from: https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=62a879e9-2c06-4028-8a58-5bac4e01d9ef

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2/3 trial evaluated the efficacy of nirmatrelvir/ritonavir in 1,120 outpatient unvaccinated patients at a high risk of a severe novel coronavirus infection compared with 1,126 placebo-treated patients. The use of nirmatrelvir/ritonavir resulted in an 88.9% (95% CI=75%, 8 of 1039 [0.8%]) reduction in the risk of severe COVID-19 (hospitalizations and all-cause mortality) vs. 66 of 1046 [6.3%] in the placebo group). There were no deaths in the nirmatrelvir/ritonavir group (0/1039), while 12 deaths (12/1046) were described in the placebo group (12/1046) by day 28 of the observation. Herewith, the incidence of AEs was comparable in both groups (22.6% and 23.9% in the study and control groups, respectively) [64].

The second study (n=180 351 patients) was conducted in January-February 2022 in Israel, when the omicron strain predominated; 2.6% of participants received nirmatrelvir/ritonavir, resulting in a reduced risk of a severe COVID-19 mortality (OR 0.54 (95% CI=0.39–0.75). This was comparable to an adequate vaccine status (OR=0.20; 95% CI=0.17–0.22). The combined antiviral drug appeared to be more effective in elderly and immunocompromised patients, as well as patients with concomitant neurological and cardiovascular diseases ($p<0.05$ for all), regardless of vaccination status [62].

Currently, there are insufficient clinical data on the use of the nirmatrelvir/ritonavir combination in children under 12 years of age (<40 kg). Gangfeng Y. et al. conducted a cohort study on a small sample of patients (n=5 – the main group, n=30 – the comparison group) aged 6-14 years with comorbidities and found out that this combination may be one of the options for treating COVID-19 in children with comorbidities. Despite the drug is recommended for use in children by the EU from 12 years and older, the efficacy and safety of the nirmatrelvir/ritonavir combination requires a further study in pediatric practice [63].

In a recent review by Saravolatz L.D. et al., the authors analyzed the available data from FDA clinical trials of oral antivirals, concluded that the nirmatrelvir/ritonavir combination showed a greater reduction in the risk of hospitalization and death than molnupiravir compared with placebo [65]. They also notified that this combination had a better safety profile (it does not have a proven teratogenic effect). The WHO considers this drug "today's best therapeutic agent for the treatment of COVID-19"[8].

In the Russian Federation, a unique technology was developed; that made it possible to combine both active ingredients (nirmatrelvir and ritonavir) into one fixed dosage form (Skyvira® LP-008056 from 20 Apr 2022)[9], which lead to the reduction of the number of tablets used, by 6 times compared to the American analogue. This provides a reduction in polypharmacy and increases the adherence and safety of therapy in general.

According to the results of the Russian open two-stage multicenter study, the considered fixed combination has a high efficacy and a favorable safety profile when used in COVID-19 patients (including the patients with comorbid pathology). The proportion of patients receiving Skyvira® who had achieved a complete recovery by the 6th day of observation was twice higher than in the comparison group. In the main group, there were no cases of COVID-19 transition to a severer course, in contrast to the patients who had received the standard therapy (8 patients were hospitalized) ($p=0.0035$, i.e. $p<0.0275$) [66].

CONCLUSION

Thus, to varying degrees, etiotropic drugs are currently available for the treatment of COVID-19 patients. Synthetic antivirals, in particular favipiravir, molnupiravir, remdesivir, and nirmatrelvir/ritonavir, have the largest evidence base for efficacy and safety. In the latest version, in addition to the above, the 16th one of the Russian interim recommendations for the prevention, diagnosis and treatment of a novel coronavirus infection (dated 18 Aug 2022), the following immunotropic drugs are marked: anticovid plasma, monoclonal antibodies and intranasal interferon alfa, umifenovir and the original domestic development – a MIR 19 preparation (synthetic small interfering ribonucleic acid, siRNA)[10]. It should be notified that both the search for new effective and safe etiotropic drugs for the COVID-19 treatment as well as the collection and analysis of post-registration data on the drugs already used in clinical practice, are being continued.

[8] WHO recommends highly successful COVID-19 therapy and calls for wide geographical distribution and transparency from originator, 22 April 2022 Statement, Geneva. Available from: https://www.who.int/news/item/22-04-2022-who-recommends-highly-successful-covid-19-therapy-and-calls-for-wide-geographical-distribution-and-transparency-from-originator.

[9] Russian State Register of Medicines. Instructions for Skyvira®. Available from: https://grls.rosminzdrav.ru/Grls_View_v2.aspx?routingGuid=e51916eb-403a-40a7-adef-0e0421269063

[10] Interim guidelines "Prevention, diagnosis and treatment of a new coronavirus infection (COVID-19)" Version 16 (18.08.2022). Available from: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/060/193/original/%D0%92%D0%9C%D0%A0_COVID-19_V16.pdf

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Table 1 – Preparations for etiotropic COVID-19 therapy

Drug groups	INN	Mechanism of action	Brief information on efficacy and safety	References
Immunological preparations	Anticovid Plasma	Antiviral (virus-neutralizing action), antibody-dependent cellular cytotoxicity, complement activation and phagocytosis	Efficacy in patients with severe COVID-19 is 76-90%. Safety: serious adverse events were observed in <1% of patients in the first 4 hours after infusion.	11–21
	Intravenous immunoglobulin	Inhibitor of pro-inflammatory complement cytokine cascade activation, dendritic cell differentiation and activation, and neutrophil activation	Efficacy in patients with ARDS due to COVID-19: no improvement in clinical outcomes (on day 28); association with a slight increase in the incidence of thromboembolic complications was found out.	22–24
	Interferons	Block virus replication via stimulation of antiviral immunity	Hospitalized patients with COVID-19 and respiratory failure had 3.8 times lower levels of interferon-α compared with control group, while improvement of patients' condition was accompanied by an increase in the level of blood interferon-α	25, 26
	Double stranded RNA sodium salt	Inducer of IFN-α (lymphocytic) and IFN-β (fibroblast)	Stimulates formation of endogenous IFN I (IFN-α, IFN-β) and IFN II (IFN-γ) types, which are the most important cytokines of immune response, induce differentiation of myeloid cells, stimulate phagocytosis of neutrophils and macrophages, activate natural killers, enhance T-helper a Th1-type response thus trigger an innate and adaptive immune response.	29
Drugs that block the entry of the virus into the cell	Umifenovir	Blocks virus penetration into "host cells" by inhibiting fusion of the virus cell membrane lipid envelope	Efficacy in patients with COVID-19: higher incidence of negative PCR results on day 14 of illness (OR=1.27; 95% CI=1.04–1.55) compared with control group; no association with reduced risk of COVID-19 progression, clinical improvement, and reduced length of hospital stay	30–32
Drugs that interfere with viral replication	Favipiravir	Inhibitor of SARS-CoV-2 RNA-dependent RNA polymerase complex by binding to its catalytic domain and preventing incorporation of nucleotides for viral RNA replication, leading to increased mutation rates and possible "lethal mutagenesis"	Efficacy of favipiravir in hospitalized COVID-19 patients according to meta-analysis: faster elimination of virus in favipiravir group – on average, on day 5 (OR=1.60; p=0.02), earlier decrease in temperature – on average on days 3–4 (OR=1.99; p <0.01), improvement of X-ray picture in the lungs (OR=1.33; p <0.01) and earlier discharge from hospital (OR=1.19; p <0.01). Efficacy of Areplivir® for parenteral administration in hospitalized patients with moderate and severe COVID-19: improvement in clinical status by 2 or more points on WHO scale by visit 3, was observed in 56.86% of patients, and in control group (patients receiving standard therapy) – in 28.04% (p <0.0001).	34–45
	Remdesivir	SARS-CoV-2 RNA-dependent RNA polymerase enzyme inhibitor	Meta-analysis of 4 studies involving 7 324 patients hospitalized with COVID-19: use of remdesivir compared with control group did not lead to a decrease in mortality (OR=0.92; 95% CI=0.79–1.07; p=0.30)	46–56
	Molnupiravir	Prodrug, N-hydroxycytidine analogue, which is phosphorylated to form N-hydroxycytidine triphosphate and integrated into viral RNA with the help of RNA polymerase, leading to accumulation of mutations in virus genome and "lethal mutagenesis"	MOVe-OUT study (n=1,433): lower risk of hospitalization or death in molnupiravir group (6.8%) compared with placebo (9.7%) (95% CI=5.9–0.1%). Efficacy of molnupiravir in outpatients with COVID-19 (n=240): 4-fold reduction in the risk of worsenig the disease course by week 2 of the study compared with standard therapy (p=0,0149); in 71.67% of patients treated with molnupiravir, SARS-CoV-2 RNA in a swab from the nasopharynx and/or oropharynx was not determined on already days 6-7 from the start of therapy; there were no cases of therapy discontinuation or changes in the study drug dose due to AEs development.	57–61
	Nirmatrelvir/ritonavir	SARS-CoV-2 3-chymotrypsin-like cysteine protease inhibitor	EPIC-HR study in COVID-19 outpatients (n=1120): 88.9% (95% CI=75%, 8 out of 1039) reduction in the risk of developing severe COVID-19 (hospitalizations and all-cause mortality) (95% CI=75%, 8 out of 1039 [0.8%]) vs. 66 of 1046 [6.3%] in placebo group). Efficacy of nirmatrelvir/ritonavir in COVID-19 outpatients: proportion of patients who achieved complete recovery by day 6 of observation was twice as many than in the comparison group; in the main group, there were no cases of transition of COVID-19 to a severer course, in contrast to patients receiving standard therapy (8 patients were hospitalized) (p=0.0035, i.e. p <0.0275).	62–66

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