Antiviral treatments for unvaccinated patients against SARS-CoV-2

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SUMMARY

Antiviral treatments for unvaccinated patients against SARS-CoV-2

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Vaccination is the primary procedure to reduce the spread of SARS-CoV-2 infection. Unfortunately, the number of vaccinated people is still too small to achieve the effect of herd immunity. The new antiviral drugs are expected to be an effective therapeutic option for the unvaccinated. In addition to the already proven lopinavir/ritonavir, favipiravir, remdesivir, the newly introduced molnupiravir and nirmatrelvir may be a new therapeutic option, also as prophylactic treatment.

Key words: *SARS-CoV-2, antiviral drugs, molnupiravir*

STRESZCZENIE

Leczenie przeciwwirusowe dla niezaszczepionych chorych przeciwko SARS-CoV-2

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Podstawowym postępowaniem mającym na celu ograniczenie szerzenia się zakażenia wywołanego przez SARS-CoV-2 jest prowadzone szczepienie. Niestety liczba zaszczepionych jest wciąż zbyt mała, aby uzyskać efekt odporności zbiorowej. Nowe leki przeciwwirusowe mają stanowić skuteczną opcję terapeutyczną dla niezaszczepionych. Obok sprawdzonych już lopinawiru/ritonawiru, fawipirawiru, remdesiwiru nowo wprowadzany molnupirawir i nirmatrelwir mogą stanowić nową możliwość terapeutyczną, w tym także jako leczenie profilaktyczne.

Słowa kluczowe: *SARS-CoV-2, leki przeciwwirusowe, molnupirawir*

The infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been responsible for over 352 million confirmed cases and 5.6 million deaths worldwide [15]. For this reason new therapies are needed to reduce the risk of progression of coronavirus disease (COVID-19). Patients with comorbidities are particularly at risk, including those suffering from diabetes, obesity and severe cardiovascular diseases.

New therapies should take into account the pathomechanism of SARS-CoV-2 infection and the stage of the disease. It has been proven that it is possible to control SARS-CoV-2 infection with drugs that block the binding of the viral spine to the cellular receptor, and thus reduce the possibility of the virus entering the cell. In turn, at a later stage, after its penetration into the cell, it is possible to inhibit its multiplication by blocking virus replicases [4]. The effectiveness of azithromycin, arechin, methylprednisolone and ciclesonide in controlling inflammation caused by SARS-CoV-2 infection has been confirmed in treated patients with symptoms of COVID-19 on an outpatient basis [10]. The use of the assessed drugs should take into account the time of onset of SARS-CoV-2 infection and the severity of the disease course, including comorbidities.

LOPINAVIR / RITONAVIR

Lopinavir/ritonavir is a specific composition of lopinavir, which is an inhibitor of viral aspartate protease (HIV) type 1, and ritonavir that increases the half-life of lopinavir by inhibiting cytochrome P450 [2]. The drug was previously approved for the treatment of HIV and now it was known that lopinavir/ritonavir exert an antiviral effect on SARSCoV-2 *in vitro* [17]. The efficacy and safety of the drug was evaluated in 245 patients in a retrospective study and randomised

study [12]. Unfortunalely, in 176 hospitals in the UK, patients admitted to hospital with COVID-19 were treated with lopinavir/ritonavir (400 mg and 100 mg), but it was not associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death [11].

FAVIPIRAVIR

Favipiravir is an inhibitor of RNA polymerase and is active against SAR-COV-2 *in vitro* (fig.1). In a trial the patients were administered 1,600 mg of the drug twice daily on day 1, followed by 600 mg twice daily from day 2 to day 5. Suspensions of favipiravir tablets were administered through a nasogastric tube. The clinical results were discussible [6].

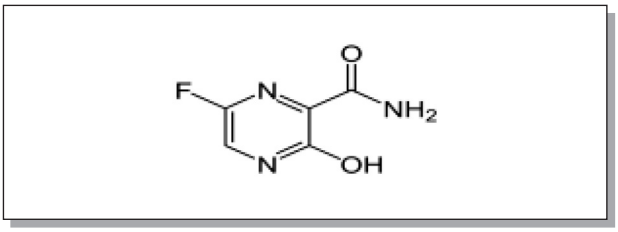

Figure 1. Favipiravir

Favipiravir has a wide range of activity against many single-stranded RNA viruses. For this reason the drug may be a promising candidate for use against SARS-CoV-2 infection [5].

REMDESIVIR

Remdesivir (GS5734) is an inhibitor of RNA polymerase with *in vitro* activity against multiple RNA viruses, including *Ebola* virus. The therapeutic studies demonstrated clinical effectiveness of remdesivir in COVID-19 patients by shortening time to clinical recovery, and hospital stay [9]. Remdesivir can be regarded as a potential therapeutic agent against COVID-19.

MOLNUPIRAVIR

Pharmacokinetic studies. Molnupiravir (Lagevrio, Merck) (fig. 2a) has activity against SARS-CoV-2 and other RNA viruses, and acts by inhibiting RNA-dependent RNA-polymerase (RdRp) of SARS-CoV-2 to induce RNA mutagenesis [7]. It is a small-molecule ribonucleoside prodrug of N-hydroxycytidine (NHC) [3,14], which is orally administered. Subsequently, NHC molecule is phosphorylated intracellularly to NHC triphosphate (fig. 2b) and is incorporated into viral RNA by viral RNA polymerase. As a result of these changes, the viral polymerase is misdirected to incorporate either guanosine or adenosine during viral replication, which causes deleterious errors of the viral genome to accumulate. It means that the newly created virus is noninfectious and unable to replicate [8,13].

Molnupiravir was developed by scientists at Emory University in the US and was originally intended to treat alphavirus infections like seasonal flu, but due to COVID-19, the testing spectrum was focused on SARS-CoV-2 infections [7]. In preclinical studies of molnupiravir in an animal model, oral efficacy of molnupiravir has been demonstrated against coronaviruses, including SARS-CoV and MERS-CoV [13].

The pharmacokinetic profile of molnupiravir was evaluated after single and multiple dose administration in a randomised, double-blind, placebo-controlled study in subjects 19-60 years of age. The study showed that ingested food decreased the rate of drug absorption, but molnupiravir was well absorbed in the plasma in a concentration range of 50-1600 mg in a dose-dependent manner. Molnupiravir was found to be quite safe at a dose from 50 to 1600 mg, and its persistence time in plasma was dose-related and was 7.08 hours. It was assumed that the tolerated dose should be 50-800 mg administered twice a day for five days [7].

Clinical studies. The efficacy of molnuprivir was assessed in unvaccinated adults with mild-to-moderate COVID-19. The patient qualification to the MOVe-OUT phase 3 trial was performed according to

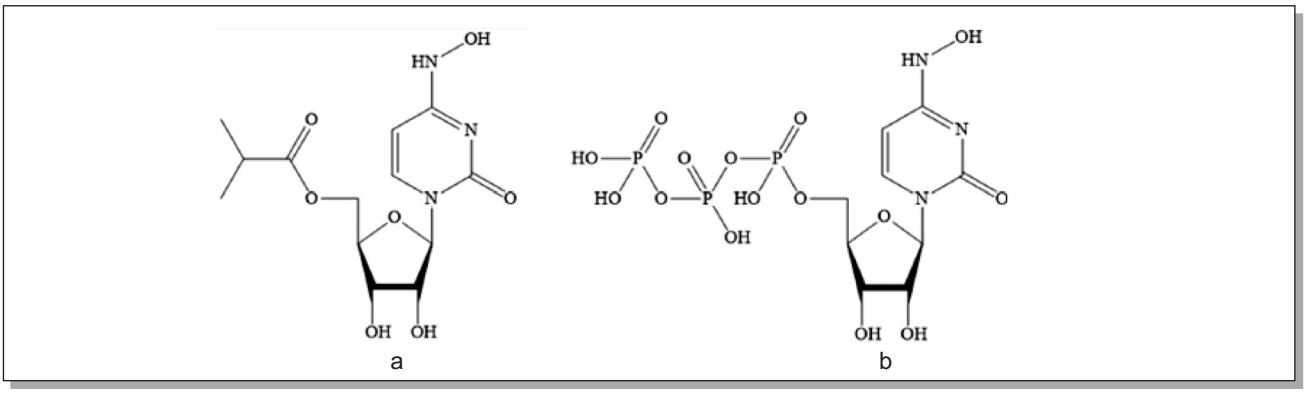

Figure 2. a – Molnupiravir, b – N-hydroxycytidine triphosphate

the WHO criteria [16]. The main inclusion criterion for the study was confirmation of SARS-CoV-2 infection in the diagnostic test before no more than 5 days, as well as the presence of at least one risk factor for COVID-19, including: age >60 years, active neoplastic process, obesity, diabetes, COPD and heart failure. Vaccination status was reported by the patients and the presence of baseline SARS-CoV-2 nucleocapsid antibodies was assessed centrally [1].

Molnupiravir was administered to 1433 participant in 107 sites in 20 countries as 800 mg (four 200 mg capsules) or identical placebo, orally twice daily for 5 days. Of all the participants, 716 were assigned to receive molnupiravir and 717 to receive placebo.

The efficacy of molnupiravir in unvaccinated patients infected with SARS-CoV-2 was expressed in a reduction in the number of hospitalizations compared to those in a placebo group (7.3% vs.14.1%) and the number of deaths (6.8% vs.9.7%). Adverse events were reported in over 30% of the analyzed subjects. It should be emphasized that in the analyzed groups of patients the main variant of SARS-CoV-2 was delta (>30%) and mu (B.1.621) variant identified in Columbia (>10%) [7].

NIRMATRELVIR

Nirmatrelvir (Paxlovid, Pfizer) acts as a SARS-CoV-2 protease inhibitor and is active against all clinically significant virus variants to date. It has been documented in performed studies that nirmatrelvir boosted with the CYP3A inhibitor ritonavir is able to reduce rates of hospitalization and death by almost 90% in unvaccinated high-risk adult patients with mild-to-moderate COVID-19 [18].

The recommended dosage is based on administration of two 150 mg nirmatrelvir tablets and one 100 mg ritonavir tablet twice daily for 5 days. In the case of symptoms of renal failure, the doses of drugs should be reduced, and in the case of severe liver disease, they should not be used.

Initial drug evaluations are encouraging, especially as they are targeted at unvaccinated people. You still have to wait for the full assessment.

SUMMARY

Management of patients infected with SARS-CoV-2 should be based on a known pathogenesis of this infection. At an early stage of contact with SARS-CoV-2, it is fully justified to block its penetration into human cells. For this reason, antiviral drugs are designed to reduce the penetration of the virus into the tissues and, secondly, to inhibit its multiplication.

The presented antiviral preparations show expected effects, which has been confirmed by the conducted research. This is of particular importance in the treatment of people infected with SARS-CoV-2 who have not been vaccinated. Molnupiravir creates a new therapeutic option; as an orally administered prodrug, it inhibits the RNA-dependent RNA-polymerase (RdRp) of SARS-CoV-2. For this reason, it is perceived as a prophylactic preparation against SARS-CoV-2 infection.

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The above article was published after the author's death.
Prof. Tadeusz Plusa, MD, was an outstanding specialist in the field of internal diseases, lung diseases and allergology, mentor to many generations of Polish allergologists and pneumonologists.