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REVIEW PAPER/*PRACA POGLĄDOWA*

Oral anti-COVID-19 drugs that were recently evaluated by FDA or EMA: a review

Przegląd doustnych leków przeciwko COVID-19, zaakceptowanych lub w trakcie akceptacji przez FDA lub EMA

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ABSTRACT

COVID-19 is an infectious disease that is caused by coronavirus SARS-CoV-2. As the time passed it became clear that, aside from the vaccines, other efficient methods of fighting the disease are urgently needed. Among the whole list of medicines used to treat COVID-19, those which are administered orally have a great advantage. The aim of this paper is to present the current knowledge about the recently investigated oral medications for COVID-19. The authors present molnupiravir (Lagevrio), baricitinib (Olumiant) and ritonavir + PF-07321332 (Paxlovid). All of these drugs have been registered recently or are waiting for authorization by EMA or FDA. During the study, the authors learned that huge progress was made, nevertheless, more studies are needed, especially in the field of side effects and drug-drug interactions of the considered substances.

KEY WORDS

COVID-19, drugs, oral, pills, molnupiravir, beta-d-N4-hydroxycitidine, eidd-2801, mk4482, baricitinib, ritonavir, PF-07321332, nirmatrelvir.

STRESZCZENIE

COVID-19 jest chorobą zakaźną wywoływaną przez koronawirusa SARS-CoV-2. Czas pokazał, że stosowanie szczepionek może znacząco ograniczyć liczbę zgonów z tego powodu. Niezbędny jest jednak dostęp do leków przeciwirusowych, które są ratunkiem dla pacjentów niezaszczepionych lub nietworzących odpowiedzi immunologicznej anty-SARS-CoV-2. Autorzy w niniejszej pracy dokonali przeglądu wszystkich leków, które są aktualnie rejestrowane w tym wskazaniu. Dane z badań klinicznych są zachęcające. Konieczne są jednak dalsze badania, w szczególności oceniające bezpieczeństwo tych leków.

SŁOWA KLUCZOWE

COVID-19, leki doustne, molnupiravir, beta-d-N4-hydroksycytydyna, eidd-2801, mk4482, barycytynib, rytonawir, PF-07321332, nirmatrelwir.

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INTRODUCTION

It has been almost 2 years since WHO declared a COVID-19 pandemic [1]. As the time passed it became clear that, aside from the vaccines, other efficient methods of fighting the disease are urgently needed. Currently there is a whole arsenal of medicines used to treat COVID-19, but those which are administered orally have a great advantage. They could be a chance for the countries with limited access to vaccines [2]. The drugs and their early administration can bring hope to the patients who cannot be vaccinated. Moreover, early treatment by lowering the number of hospitalizations could be helpful to cease the medical care crisis in many countries [3]. Scientists used the AI technology, computational screening and numerous clinical trials to reveal the drugs we could possibly use against COVID-19.

The aim of this paper is to present the current knowledge of the recently evaluated oral medicines for COVID-19. The authors present molnupiravir (Lagevrio), baricitinib (Olumiant) and ritonavir + PF-07321332 (Paxlovid). All of these drugs have been considered recently by EMA or FDA.

MOLNUPIRAVIR, LAGEVRIO®

Molnupiravir is being developed by Merck and Ridgeback for the purposes of COVID-19 management in adult patients with a positive diagnostic test and risk factors for progression to severe COVID-19 [4].

The medicine is an isopropyl ester prodrug of the nucleoside analog β-D-N4-hydroxycytidine (NHC) [5], which is proved to interfere with the replication of multiple viruses, including the SARS-CoV-2 [6–15]. Its active metabolite, β-D-N4-hydroxycytidine-triphosphate [16], targets the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which mediates replication and transcription of the coronavirus genome and therefore causes mutagenesis, which eventually leads to the impairment of the replication [17–22]. Moreover, the studies show that molnupiravir has a high genetic barrier to viral resistance [6]. It was proved effective in animal models [23–29] and safe in phase 1, 2 and 3 of the clinical trials [30–38]. There are still four clinical trials ongoing, according to www.clinicaltrials.gov (as at December 12, 2021). Moreover, it is not a potent agent for oxidational stress, which increases its safety [39]. However, there are still some concerns about mutagenesis in mammalian cells [40, 41]. At first Merck reported that the drug can reduce the risk of hospitalization and death by 50% [42, 43], nevertheless, the latest update on MOVe-OUT study shows that the relative risk of hospitalization is lower than expected and is reduced to 30% [4]. This study involved 1433 participants. Molnupiravir was proved to reduce hospital admission or death from 9.7% in the placebo group (68/699) to 6.8% (48/709) in the molnupiravir group. Absolute risk reduction is 3.0% (95% confidence interval (CI): 0.1–5.9; nominal p-value = 0.0218). 10 patients died – 9 from the placebo group and 1 from the molnupiravir group [3, 44].

This drug currently is under evaluation by EMA [45], but it is authorised in England [46] with recommended dosage of 800 mg twice a day. According to EMA recommendations, treatment course should start within 5 days from the onset of the symptoms and should last 5 days. Most common adverse effects are: dizziness, headache, diarrhea, nausea with mild to moderate severity [47].

Molnupiravir was discussed by FDA on November 30, 2021 for Emergency Use Authorization (EUA) in adults [44]. Treatment course recommendations are similar to those from EMA [48].

BARICITINIB, OLUMIANT®

Baricitinib is a Janus associated kinase (JAK) inhibitor, which was primarily used for treatment of rheumatoid arthritis [49–51]. It has a good safety and efficacy profile, despite some concerns [52–55]. Baricitinib is able to modulate the cytokine storm through the JAK-STAT pathway [56–62]. Artificial Intelligence algorithms suggested its utility in treating COVID-19 [63–66] and it has been proved effective in animal models [67, 68].

In most cases, the drug contributes to the reduction of mortality rate and recovery duration in patients with moderate or severe COVID-19 pneumonia [69–74], either along with other drugs or alone [75–82]. Its effectiveness has been shown in pediatric patients with severe COVID-19 as well [83]. Moreover, baricitinib is proved to cease the progression to severe pneumonia [84]. The drug may not lower the mortality rate in patients with severe pneumonia and on the course of tocilizumab and steroids at the same time [85]. Combined with steroids, baricitinib also seems to be as efficient as anakinra when it comes to the mortality rate [86]. In spite of concerns on its safety [87–93], the meta-analyses generally show that baricitinib is suitable for treatment of COVID-19 [94–103].

EMA first authorised baricitinib in February 2017 for rheumatoid arthritis and the drug is currently under evaluation for marketing authorization for the treatment of COVID-19 [104]. The drug comes in 2 mg or 4 mg pills, and its main adverse effects are: upper respiratory tract infections, hypercholesterolemia, herpes zoster and herpes simplex infections, gastroenteritis, urinary tract infections, thrombocytosis, headache, abdominal pain, rash, acne and increase in AKT and creatine phosphokinase [105, 106]. Remarkably, pulmonary embolism and deep vein thrombosis might occur in more than 1% of the patients [107].

Baricitinib is authorised for emergency use along with remdesivir by FDA [106, 108, 109] in 1 mg and 2 mg pills. It can be used in adults and children older than 2 years, who require oxygen supplementation, invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [110]. The treatment course involves the drug intake once a day for 14 days [111] with the recommended dosage of 2 mg for patients under 9 years old and 4 mg for patients older than 9 years [107].

PAXLOVID®

Paxlovid is a drug produced by Pfizer and it consists of 2 active substances: PF-07321332 and ritonavir. The drug is designed to be administered orally and is proved to be successful in clinical trials [112]. PF-07321332 is administered along with ritonavir to increase its half-life and therefore its level in the patients' blood [113–115].

The manufacturer claims that this drug significantly reduces hospitalization and death, based on an interim analysis of the Phase 2/3 EPIC-HR randomized, double-blind study of non-hospitalized adult patients with COVID-19. The patients had high risk factors for the illness progression. The analysis of 1219 patients showed an 89% reduction in the risk of COVID-19-related hospitalization or death in patients who received treatment within three days from the symptoms onset. The drug was compared to placebo [113]. The latest update on Paxlovid's clinical trials seem to confirm its effectiveness. Moreover, Pfizer informs that risk of hospitalization or death is reduced by 88% in patients treated within five days of the symptoms onset. By day 28 no deaths were reported in the group of patients who received Paxlovid and 12 deaths in the placebo group. Relative risk reduction was 94% in patients 65 years of age and older. The manufacturer claims that the drug is potentially effective against the newest variants of COVID-19 [114]. As at December 15, 2021 there was no information about the recommended dosage. In the paragraphs below, the authors review information we have on PF-07321332 and ritonavir. Paxlovid is still waiting to be authorised for emergency use by EMA and FDA [116, 117].

PF-07321332 – NIRMATRELVIR

PF-07321332 is a drug that is predicted to be really useful in the treatment of COVID-19 [115, 118]. It is a 3CLpro inhibitor, which gives it the ability to treat coronaviruses. 3CLpro is a viral protein essential for SARS-CoV-2 replication [119, 120]. Its usefulness has been evaluated by computational analyses [121–123]. As at December 13, 2021 the drug was under 6 clinical trials (according to www.clinicaltrials.gov).

RITONAVIR

Ritonavir is a drug used for the treatment of HIV [124]. It has been suggested by AI as well [125–128]. It is mostly used along with lopinavir to prolong its half-life with good *in vitro* effects [129, 130], but the results in COVID-19 therapy mostly show that the use of this combination may be not satisfactory [131–138]. They do not reduce the 28-day risk of death, disease progression and hospitalization [139]. Their main adverse reactions are gastrointestinal symptoms, metabolic derangements (hypercholesterolemia, hyperglycemia), hematological and cardiac disorders [140, 141]. Twelve meta-analyses show that treatment with lopinavir/ritonavir is not significantly beneficial [142–153]. Five meta-analyses state that treatment with lopinavir/ritonavir is possibly useful, but their authors highlight that their papers may be biased by insufficient amount of evidence [154–158]. One suggests that the treatment is very likely to be beneficial for patients [159].

Current (as at December 13, 2021) WHO guidelines do not recommend the use of lopinavir/ritonavir for treatment of COVID-19 [160].

DISCUSSION

As the time passes, the need for orally administered anti-viral drugs gradually increases [161]. The perfect medicament should be safe, well-tolerated, easily available, economically efficient and useful as a prophylaxis in patients who are likely to contract the disease. The pursuit for the perfect anti-COVID-19 drug is still ongoing, but the first registrations by FDA/EMA of oral drugs give us hope that we are going in the right direction.

Molnupiravir is a drug that can possibly be an important tool in treatment of COVID-19, due to its unique activity on SARS-CoV-2 [162]. Its safety and efficacy profile, high resistance barrier and capability of reducing the number of hospitalizations will surely give this drug its

own decent place in the anti-COVID-19 arsenal. The authors are looking forward to learning the newest information after the drug release. So far, the main disadvantage of molnupiravir seems to be its predicted price, which may limit the access to the drug [2].

Baricitinib has entered the list of anti-COVID-19 drugs with the help of observational studies and bioinformatics [163–165]. The fact that the drug has been used earlier is its great advantage – its adverse effects and drug-drug interactions are relatively well known. Moreover, due to its former usage, it is easily available in many countries. Despite the price of the therapy, its usage has been proved to be cost-effective [166–168].

There is few information about Paxlovid yet, but so far the drug manufacturers can be satisfied with the early results of their studies. Combining PF-07321332 with ritonavir as a booster is an interesting decision to increase the drug's efficacy. If Paxlovid's effectiveness is confirmed in the following clinical trials, it has a solid chance to become one of the best medicines for COVID-19. The authors are going to observe the newest information with great interest. Moreover, Paxlovid may be useful as a prophylaxis [169]. Unfortunately, this drug is also predicted to be relatively expensive [2].

To summarize, all of the drugs seem to be very promising and each one of them could possibly find its own place in the treatment of COVID-19. Nevertheless, more studies are needed, especially in the field of side effects and drug-drug interactions – such studies may show the limitations of these medicaments.

CONCLUSIONS

Introduction of the oral anti-COVID-19 drugs can indeed change the course of the pandemic. However, the first place for the perfect oral anti-COVID-19 drug still remains open. The authors are going to observe the incoming papers on oral antiviral treatment with great interest.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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