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LETTER TO THE EDITOR

Pill versus vaccine for COVID-19: Is there a genuine dilemma?

Keywords COVID-19; Oral antivirals; Pandemic; Vaccines

Dear Editor

On March 11 2020 the World Health Organization (WHO) upgraded officially the awareness level over COVID-19 from a Public Health Emergency of International Concern to a pandemic. A coordinated attempt of the scientific community accelerated the SARS-CoV-2 genome and structural analysis, shedding light into the virological properties, biology of the disease and pathophysiology of infection, and set the grounds for the vaccine development process. Vaccines are an efficient approach to achieve widespread immunity, reducing disease morbidity and mortality and raising the selective pressure plateau, limiting the formation of novel viral variants, thus constituting the cornerstone of disease-preventive strategies.

Currently, the viral-vector and the nucleic-acid vaccines for COVID-19 have been extensively utilized into clinical practice in Western populations, with a high effectiveness on preventing severe disease and death. The most widely used vectors are the adenovirus serotype 26 (Ad26.CoV2.S) and the chimpanzee adenovirus (ChAdOX) carrying the encoding gene of spike protein, which is effective to initiate innate, cellular and humoral immune responses [1]. The only approved nucleic—acid vaccines for COVID-19 at the moment are mRNA vaccines, which employ a new approach to transfer the S protein-expressing mRNA into lipid nanoparticles directly to the cytoplasm and have a favorable side-effect profile [1]. Additionally, alternative vaccines are under investigation in preclinical and clinical trials.

On the other hand, different oral antiviral treatments recently have started to emerge as weapons in our therapeutic artillery against COVID-19. Presently, there are no FDA- or EMA-approved oral agents for outpatient therapy, while only Molnupiravir has been licensed by the UK medicines regulator [2]. On October 11, 2021, Merck in cooperation with Ridgeback Biotherapeutics announced that Molnupiravir, an oral nucleoside analogue, was submitted for Emergency Use Authorization (EUA) to the U.S. Food and Drug Administration (FDA). Their application is based on encouraging results from a phase 3 clinical trial of non-hospitalized adult patients with mild-to-moderate disease at increased risk for severe COVID-19, which demonstrated that a 5-day course of Molnupiravir, 800 mg twice daily within 5 days of symptom onset, reduced approximately 30% the risk of hospitalization or death. This agent is also being evaluated for post-exposure prophylaxis in the context of prevention of COVID-19 spread [3]. Molnupiravir is a prodrug that can be metabolized into a ribonucleoside analog, whose active ribonucleotide form can be incorporated into viral RNA, forcing it to lethal mutagenesis during replication [4]. There are theoretical concerns about its potential risk for genotoxicity, as its deoxyribonucleotide metabolite is mutagenic to host cell DNA [5]. However, available data until now indicate that the drug is not genotoxic in *in vivo* mammalian systems. PF-07321332 (Pfizer) is another oral antiviral, which is currently evaluated in phase 3 clinical trials. It is a 3-chymotrypsin-like protease inhibitor (3CLpro) that interferes with the formation of viable viral particles [6]. It is administered in combination with ritonavir (Paxlovid, PF-07321332; ritonavir) within 5 days of symptom onset in non-hospitalized participants with symptomatic COVID-19 at increased risk of progressing to severe illness. The results of the interim analysis of the Phase 2/3 EPIC-HR study showed a reduction in the risk of hopitalization or death by 89% in high-risk outpatients [7]. A study for the assessment of Paxlovid as post-exposure prophylaxis is also ongoing. Finally, AT-527, an RNA polymerase inhibitor by Atea Pharmaceuticals in collaboration with Roche, is also assessed for outpatient treatment in a phase 3 clinical study. Other agents-candidates as oral treatments are also under investigation and results are expected in the near future.

Nowadays, vaccines represent the base of the pharmaceutical COVID-19 prevention pyramid, as they are widely effective in decreasing risk for severe disease, hospitalization and transmission. The mRNA vaccines present a plethora of advantages, such as high stability, ease of mass production and distribution, and a safe profile without the risk of genomic alterations [8]. It is also of determining importance that they can be easily modified in order to target mutated variants, with limited financial disbursement in a relatively short time. Finally, further analyses have demonstrated that the wide use of vaccines is a cost-effective preventive measure, especially when compared to other prevention strategies [9]. One of the highlighted drawbacks is the need for continuous evaluation of their effectiveness and duration of protection that they provide [8]. It's worth noting that serious side effects have been reported after vaccination, including immune-mediated thrombotic thrombocytopenia accompanying viral-vector vaccines and peri- and myocarditis after mRNA vaccination. Both conditions are rare and manageable, if detected promptly, therefore their risk can be outweighed by the benefits of widespread vaccination.

Table 1 The main advantages and disadvantages of vaccines and oral antivirals for COVID-19.

	Advantages	Disadvantages
Vaccines	Efficacy in preventing transmission, hospitalizations and severe complications of the disease	Need for continuous evaluation of their efficacy and duration of immunity Decreased efficacy against specific variants of SARS-COV-2 and in some populations of immunocompromised individuals
	High stability, ease of mass production and distribution mRNA vaccines: modifiable for inclusion of mutated variants Favorable benefit-risk profile Approved for administration in pregnant women Cost-effective prevention strategy No risk of genomic alterations	
Oral Antivirals	Convenient and accessible outpatient treatment	Need for further data regarding their efficacy
	Use for post-exposure prophylaxis Molnupiravir and Paxlovid: reduction in the risk of hospitalization or death	Theoretical but unproven risk for genotoxicity with Molnupiravir
		Tested only in the adult population No data on pregnant women
	Safe profile regarding short-term adverse effects	
		Inadequate data on viral resistance potential

The newly introduced oral antivirals may provide a convenient and easily accessible treatment option for outpatients. Their utilization has been proposed as treatment in the pre-clinical setting and as post-exposure prophylaxis. Molnupiravir and Paxlovid have demonstrated a significant reduction of hospitalizations and morbidity in symptomatic patients. Clinical trials have reported a safe short-term side effect profile but more data needs to be accumulated in order to assess their full spectrum of adverse events and their effect on disease transmission from COVID-19 patients to uninfected individuals. Significant limitations of the clinical trials include the non-representative sample size, the inclusion of adults only and the exclusion of pregnant women, where vaccination has been shown to be safe. Our knowledge is still insufficient as regards their cost-effectiveness and drug resistance potential, given the fact that a multitude of mutated variants could emerge.

Summarizing the accumulating data about COVID-19 treatment and prevention options, it becomes evident that both the vaccines and oral antiviral medications come with significant benefits, as well as worth-mentioning limitations. Their main pros and cons are summed up in Table 1. In addition, it should be accentuated the importance of the non-pharmaceutical interventions (NPIs) in the control of the pandemic. Social distancing, masks, proper indoor ventilation, limitation of social contact, hand hygiene, surface cleaning, contact tracing and isolation, and quarantine of infected individuals are well-studied examples of an ever-growing list of NPIs. Accurately balanced, stratified health policies should be legislated in order to avoid social polarization [10].

In conclusion, in our perspective the ''vaccine vs pill'' debate turns out to be a false dilemma, as it is evident that both pharmaceutical options, vaccines and oral antivirals, have unique, distinct but complementary roles in the management of the COVID-19 pandemic.

Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

Informed consent and patient details

The authors declare that the work described does not involve patients or volunteers.

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References

[1] Murugan C, Ramamoorthy S, Guruprasad K, Murugan RK, Sivalingam Y, Sundaramurthy A. COVID-19: A review of newly formed viral clades, pathophysiology, therapeutic strategies and current vaccination tasks. Int J Biol Macromolecules 2021.
[2] First oral antiviral for COVID-19, Lagevrio (molnupiravir), approved by MHRA. MHRA; 2021, https://www.gov.uk/

government/news/first-oral-antiviral-for-covid-19-lagevrio-molnupiravir-approved-by-mhra [accessed November 2021].
[3] Merck and Ridgeback Announce initiation of a rolling review by the European Medicines Agency for Molnupiravir, an Investigational Oral Antiviral Medicine for the Treatment of COVID-19 in Adults. Merck; 2021, https://www.merck.com/news/merck-and-ridgeback-announce-initiation-of-a-rolling-review-by-the-european-medicines-agency-for-molnupiravir-an-investigational-oral-antiviral-medicine-for-the-treatment-of-covid-19-in-adults/ [accessed 10 November 2021].
[4] Kabinger F, Stiller C, Schmitzová J, Dienemann C, Kokic G, Hillen HS, et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. Nat Struct Molecular Biol 2021;28:740—6.
[5] Zhou S, Hill CS, Sarkar S, Tse LV, Woodburn BMD, Schinazi RF, et al. β-d-N4-hydroxycytidine Inhibits SARS-CoV-2 through lethal mutagenesis but is also mutagenic to mammalian cells. J Infect Dis 2021;224:415—9.
[6] Vandyck K, Deval J. Considerations for the discovery and development of 3-chymotrypsin-like cysteine protease inhibitors targeting SARS-CoV-2 infection. Curr Op Virol 2021;49:36—40.
[7] Pfizer's Novel COVID-19 oral antiviral treatment candidate reduced risk of hospitalization or death by 89% in interim analysis of phase 2/3 EPIC-HR study. Pfizer; 2021, https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidate [accessed 10 November 2021].
[8] Rahman MA, Islam MS. Early approval of COVID-19 vaccines: pros and cons. Hum Vaccines Immunother 2021;17:3288—96.
[9] Kohli M, Maschio M, Becker D, Weinstein MC. The potential public health and economic value of a hypothetical COVID-19 vaccine in the United States: use of cost-effectiveness modeling to inform vaccination prioritization. Vaccine 2021;39:1157—64.
[10] Escandón K, Rasmussen AL, Bogoch II, Murray EJ, Escandón K, Popescu SV, et al. COVID-19 false dichotomies and a comprehensive review of the evidence regarding public health, COVID-19 symptomatology, SARS-CoV-2 transmission, mask wearing, and reinfection. MC Infect Dis 2021;21:710.

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