Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Enfermedades Infecciosas y Microbiología Clínica xxx (xxxx) xxx–xxx

Enfermedades Infecciosas y Microbiología Clínica

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Scientific letter

Generalized use of Nirmatrelvir plus ritonavir (Paxlovid): Raising concerns

Uso generalizado de Nirmatrelvir más ritonavir (Paxlovid): Algunos planteamientos

Nirmatrelvir plus Ritonavir (Paxlovid) will be used in Spain soon.[1] Although the potential effect of the drug against COVID-19 infection has biochemical explanation and has been demonstrated in several in vitro studies,[2] final acceptance arrived from the Randomized Clinical Trial (RCT) supported by Pfizer and published by Hammond et al.,[3] which was carried out in patients who were neither vaccinated nor had previously had COVID-19 infection, with a mild COVID-19 infection of less than 5 days. Despite the spectacular results of this RCT, several concerns should be considered.

First, patients with at least one risk factor for severe COVID-19 disease were selected. These risk factors were, among others, being over 60 years of age, having a Body Mass Index (BMI) greater than 25 or having one of several relatively prevalent diseases such as high blood pressure, smoking, heart disease or lung disease. It is necessary to highlight that the proportion of people with at least one risk factor in our environment is very high. More than 40% of the Spanish population would have a BMI > 25[4] or almost 20% of the population is over 65 years old,[5] which could mean an excessive number of potentially treatable patients.

Another important point to keep in mind is that the composite variable "admission or death" was chosen as outcome. Thanks to this, the Number Needed to Treat (NNT) to avoid an outcome was 18 patients (event rate in the treatment group of 0.78% vs. 6.40% in the placebo group; absolute risk reduction of 5.62%). However, when analysing events, we found that death was 18.2% of events (12/66 cases). Looking only at deaths, risk reduction was 1.15% (0% vs 1.15%) with an NNT of 87 patients. Mortality could be more useful to take decisions since many admissions may be short and perfectly assumable nowadays. Thus, it is essential to deepen into the characteristics of patients with adverse outcomes, both in terms of their comorbidities as well as the implications of such admission (stay, clinical severity, maximum need for oxygen flow or admission to the ICU), the latter being missed from the study.

It should also be noted at this point that it seems that COVID-19 disease is beginning to behave like any other viral infection with the potential effect of producing community-acquired pneumonia (CAP). An unintended fact that emerges from the article is that mortality in unvaccinated patients with risk factors in the placebo group was only 1.15%. We must not lose sight of the fact that CAP has an incidence and hospitalization rate of 4.63 and 1.64 cases per 1000 people/year in Spain,[6,7] with a mortality of 4–18% in hospitalized patients, increasing dramatically in those with one or several comorbidities,[8] and that most of them are caused by viruses.[9]

Regarding the results, it seems clear that Paxlovid has a beneficial effect in preventing worsening of COVID-19 disease in selected mild patients with less than 5 days of symptoms, which is a promising milestone in the development of antiviral agents. Despite this, prudence is needed when regulating and using this medicine. When extrapolating the data to our daily clinical practice, and despite the fact that Pfizer is already carrying out another similar RCT in vaccinated patients (EPIC-Standard Risk [SR]; NCT05011513), it is important to be aware that at the moment there is only one published RCT and that it has been carried out in unvaccinated population that had not had COVID-19 disease. In Spain, at the end of March 2022, more than 80% of the population has been vaccinated and one in four people has already overcome the disease.[10] Thus, clinicians should perform optimal risk stratification before prescribing such drug so that Paxlovid does not become inappropriately used.

It may seem obvious, but we must not forget that the process of approving new drugs requires prudence, and although at the worst of the pandemic it was necessary to practice a medicine that was not strictly based on the evidence, fact that we all remember well, our situation today is no longer critical. That is why it is more necessary than ever to recover the scepticism and critical sense usually associated with scientific methodology, as well as the individual common sense of the art and science of medical practice.

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https://doi.org/10.1016/j.eimc.2022.04.007

Please cite this article as: D. Sánchez Fabra and T. Herrero Jordán, Generalized use of Nirmatrelvir plus ritonavir (Paxlovid): Raising concerns, Enferm Infecc Microbiol Clin., https://doi.org/10.1016/j.eimc.2022.04.007

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