Paxlovid: a new antiviral drug very effective against COVID-19

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A protease inhibitor specific to the SARS-CoV-2 coronavirus, Paxlovid, shows remarkable clinical activity with a 90% decrease in hospitalizations caused by COVID-19.

Vaccines against Covid-19 have drastically reduced the devastation caused by the pandemic. However, it is difficult, if not nearly impossible, to vaccinate everyone (especially globally) and the virus is taking this opportunity to continue to spread, with more than 300,000 cases diagnosed globally every day.

It therefore seems increasingly certain that the discovery of additional means to curb the virus will be necessary to put a definitive end to the mortality caused by this pandemic.

PROTEASE INHIBITORS

Viruses are obligate parasites, which must use the enzymatic machinery of our cells to make the proteins that allow them to reproduce. In the case of the coronavirus, 29 proteins are necessary for its cycle of infection, four of which are responsible for the external structure, including the famous spicule that allows it to bind to the ACE2 receptor and enter the cell.

The other non-structural proteins, which are also essential for the replication of the virus, are synthesized in the form of long chains where the proteins are linked together in a single file.

These polyprotein chains are subsequently cut by a viral protease, which generates a series of smaller proteins, which then become able to perform their roles in the reproductive cycle of the virus.

This maturation step is a prime target for the development of antiviral agents, because by blocking the activity of the protease, it also prevents the production of a large number of proteins essential for the virus survival.

It is this principle that is the basis of modern drugs against AIDS and hepatitis C, very effective and safe therapies that have completely revolutionized the treatment of patients affected by these diseases.

SPECIFIC INHIBITOR

In 2003, Pfizer scientists quickly identified a specific inhibitor of the SARS-CoV-1 protease that was responsible for the SARS epidemic that had raged the previous year. The rather abrupt end of the epidemic (this virus was much less contagious than its current cousin was), however, put an end to the clinical development of this drug.

Almost 20 years later, however, it seems that these efforts were not in vain: after some molecular modifications made to the molecule to improve its oral bioavailability, they obtained the compound PF-07321332 (called Paxlovid by the company).

This molecule has a strong inhibitory activity against the main protease

(Mpro) of the SARS-CoV-2 coronavirus and demonstrates strong antiviral activity (1). In addition, a phase 1 study has shown that administration of the drug to human volunteers achieves plasma concentrations sufficient to block that protease *in vivo*.

The results of a phase 3 study, carried out in patients with risk factors for complications from Covid-19, have just been announced by the company and are quite spectacular: treatment with Paxlovid has decreased by 89% hospitalizations when the drug is administered within the first three days of the onset of symptoms of Covid-19 and by 85% when administered within the first five days. The superiority of the treatment over placebo was so great that the study was terminated prematurely for ethical reasons.

Overall, looking at all of the patients treated (3 and 5 days post-symptom), the data shows that nine people were hospitalized and that there were no deaths out of a total of 996 patients, compared to 68 hospitalized patients and 10 deaths in the group of 997 patients who received the placebo.

This protection is greater than that observed (50%) for another antiviral, molnupiravir, possibly because Paxlovid has been specifically designated against the coronavirus protease, while molnupiravir is a more general antiviral, initially developed against the virus of influenza.

A few additional points are worth highlighting:

1. Oral administration of Paxlovid allows for greater flexibility in its use than other drugs that must absolutely be given to patients in hospital, intravenously (eg, monoclonal antibodies);

2. The viral protease targeted by Paxlovid is a cysteine protease that has a unique mode of action, absent in humans (cleavage of the peptide chain after the amino acid glutamine), which limits potential side effects; and

3. If you count the year it took to identify the molecule in 2003, the researchers only needed 3 years to get the drug from the test tube to the bedside, a feat unique in the history of pharmacological biochemistry.

In sum, these results suggest that administering this drug to people with symptoms of Covid could prevent up to nine in ten hospitalizations and virtually eliminate illness-related deaths. These are obviously remarkable results, which could represent a turning point in our fight against the pandemic.

(1) Owen DR et al. An oral SARS-CoV-2 M pro inhibitor clinical candidate for the treatment of COVID-19. Science, (published online, Nov 2nd 2021)

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