Go behind the virus on its entry way with targeted pharmacological therapy: the inhalation route of anti SARS-Cov2 active substances.

ANTI COVID-19 INITIATIVE by Paolo Colombo and Ruggero Bettini

BACKGROUND

SARS-Cov2 is the last appeared coronavirus that developed a pandemic infection with huge number of fatal cases. No vaccines are yet available that protect from this infection. However, a number of therapeutic tactics against COVID-19 have been empirically started. According to Mehra et al., 2020, in COVID-19 illness, a structured approach to clinical is imperative (1). Such approach distinguish the phase in which the viral pathogenicity is dominant, from the phase where the host inflammatory response overtakes the pathology. Therefore, after five months of epidemic, 3-stage's progression of illness, corresponding to increasing severity with distinct clinical signs, therapy responses and clinical outcomes, has been assessed. These stages constitute the reference for investigation and proposition of effective targeted therapies (1).

Stage I is the phase where the early infection causes to most people mild or asymptomatic disease. Treatment at this level with drug having antiviral activity could prevent the progression to severe disease. Stage II (moderate) corresponds to the pulmonary involvement without (IIa) and with (IIb) hypoxia. In this stage the pulmonary disease is established with viral lung multiplication and localized inflammation. The patients develop a viral pneumonia, with cough, fever and possibly hypoxia. Now, not only antiviral drugs are required but, in particular, the inflammation has to be considered and treated. Stage III is the phase in which an extra-pulmonary systemic hyperinflammation syndrome manifests. Likely, a minority of Covid-19 patients transit to this stage where the therapy is essentially against the so called “inflammation storm”.

The stage classification highlights the importance of the immediate start of an appropriate therapy. This is particularly true at Stage I, where the limitation of the virus spreading in the organism could hinder the evolution to Stage II. At the same time, the limiting the virus replication reduces the contagiousness of the infected persons. During talking, coughing or sneezing, droplets of virus rich saliva or mucus are expelled that can be ihaled by someone else. The inhaled SARS-CoV2 deposits in the nose or throat where it enters the epithelium cells through the cell-surface receptor ACE2. The receptor is the target for the uptake by cells, where the virus uses the cell “machinery” for replication. Then, the huge number of virus replicates can move to lung from where they spread in other organs, including brain (2).
PRESENT DRUG THERAPY

No specific treatments for SARS-Cov2 have been approved to date. However, a number of pharmacologically active substances are under investigation to tackle the virus replication, including the ones authorized to treat malaria, autoimmune diseases, antiparasitic or infections caused by bacteria or other viruses. These drugs have been studied in limited clinical trials with debatable success, due to the limited number of patients involved and because “patients (were) enrolled during the pulmonary stage with hypoxia (stage IIb) when the viral pathogenicity may have been only one lesser dominant aspect of the overall pathophysiology, and host inflammatory responses were the predominant pathophysiology” (2).

Surprisingly, these clinical studies have been exclusively performed by systemic drug administration (oral or injection), whereas the virus enters the body essentially via the respiratory tract i.e., from mouth and nose. The systemic administration provides a low drug concentration at the site of infection. Actually, drug disposition could be increased by increasing the dose, but risks of adverse effects increase as well.

THE NOVEL THERAPEUTIC IDEA

Drug administration by inhalation is the way to increase the drug concentration exactly where the virus enters in contact with the body cells. The drug deposited and absorbed on the respiratory epithelium following an inhalation act, gives rise to very high local concentration, still keeping low the blood levels. This is the innovative yet simple concept that the Innovative SME intends to develop in collaboration with the researchers of the Universities of Parma and Ferrara. Since Covid-19 infects through the upper respiratory tract, the novel pharmacological treatment strike it by the same route.

The pharmaceutical technology instruments to hit the illness in Stage I and Stage IIa are in the competences of PlumeStars and the Parma and Ferrara research groups. Therefore, an inhalation product, i.e., highly respirable drug powder loaded in an appropriate inhaler, at a dose lower than oral dosage, is the novel therapeutic approach under study. Moreover, Stage I and Stage II illness differ for the location of the virus that in the Stage I is mainly in the nose or throat and in Stage II in the whole lung. This implies that, for the two different Stages, distinct inhalation manoeuvres, i.e., nasal and pulmonary, has to be studied. A very interesting aspect is that the inhalation powder, depositing the drug in the nose and throat, could be proposed as prophylactic/protective product for the people exposed to risk of infection, such as the health care providers during their professional activity.

PlumeStars is an Innovative SME, founded in Parma on a patent of University of Parma, that got the EMA and FDA orphan medicine designation for the antibiotic amikacin powder for inhalation in cystic fibrosis lung infections. The SME is the driving force of the proposal by pushing the use of its
proprietary technology for constructing engineered microparticles to provide highly respirable antiviral drug powders. Thus, the therapeutic solution for SARS-Cov2 under study by PlumeStars, consists in a drug powder for inhalation administered with a dry powder inhaler. The microparticles, deposited on the respiratory epithelium of the upper and lower airways, dissolve on site providing high local drug concentrations where the virus replicates. Such a high concentration in the infected epithelium is not attainable by systemic administration. As a further advantage, after local absorption in airway epithelium, the blood drug level remains significantly lower and therefore, safer than after oral or injection administrations.

Finally, the drugs proposed for inhalation product are known drugs that during the previous SARS infection have shown an activity against the coronaviruses. For example, the antimalarials chloroquine (3) and hydroxychloroquine, anti-parasitic ivermectin, antibiotic azithromycin or glycyrrhizine (4) are candidates for the anti SARS-Cov2 inhalation products. These substances have the advantage to be known for their toxicity and adverse effects. In addition, antivirals such as ribavirin or the newest molecules as remdesivir, can also be presented as inhalation products.

This is the planned project of PlumeStars against SARS-Cov2 infection by a pharmacotherapy approach for which the SME is looking for pre-clinical and clinical collaborations.

REFERENCES


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