Journal of Pharmaceutical Care
jpc.tums.ac.ir

Molecular Mechanisms of Galidesivir as a Potential Antiviral Treatment for COVID-19

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Received: 2020-06-25, Revised: 2020-07-06, Accept: 2020-07-07, Published: 2020-09-30

ARTICLE INFO

Article type:
Focus

J Pharm Care 2020; 8(3): 150-151.

► Please cite this paper as:
Ataei M, Hosseinjani H. Molecular Mechanisms of Galidesivir as a Potential Antiviral Treatment for COVID-19 . J Pharm Care 2020; 8(3): 150-151.

Coronaviruses are a large family of viruses spread from animals to humans and include Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) in addition to the new one called COVID-19. Nowadays, we know that these viruses transmit from person to person. Coronavirus name is because of the crown-like spike protein that they have on their envelope (1). COVID-19 causes respiratory severe problems that can lead to death (2). The International Committee on Taxonomy of Viruses named this virus as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Since the new Coronavirus has suddenly spread in Wuhan, China, it involves all around the world, and on 11 March 2020 was described as a pandemic by World Health Organization (WHO) report (3).

SARS-CoV-2 is a single-strand RNA virus that is characterized by two categories of proteins: structural proteins and non-structural proteins such as proteases and RNA dependent RNA polymerase (RdRp). RdRp is the main part of the non-structural protein 12. RdRp is a vital enzyme in the virus life cycle and is responsible for the synthesis of multiple copies of complementary RNA from the viral template RNA. Targeting this enzyme can stop the virus from multiplying and leads to virus death (2). Each base-pair nucleotide converts to triphosphate nucleotide and binds to the RdRp enzyme and RNA pattern. Therefore nucleoside antivirals are good choices for inhibition of this enzyme as they are uptaken well into cells and convert to triphosphate form by mammalian kinases. As an example, in human cell culture (in vitro) and after an IM injection in rats (in vivo), BCX4430 is well uptaken into cells and converted to triphosphate form. After an IM injection in rats, the BCX4430 intercellular level exceeds the plasma level of the pattern drug within 30 minutes, and after 24 hours, it becomes 10-100 fold more than the plasma level. So it can be used once daily to block the virus replication (4).

Currently, no clinically proven specific antiviral agent is available for SARS-CoV-2 infection (5). Galidesivir (BCX4430, Immucillin-A) is a nucleoside RdRp inhibitor drug developed by BioCryst Pharmaceuticals for treating Ebola (1). It is a broad-spectrum antiviral drug that affects the coronaviruses family and other RNA viruses such as HCV, Ebola, and Yellow fever by preventing the growth of these viruses in cell culture (5-8). As an example, by increasing the drug concentration in the Vero-E6 cell line infected with MERS-CoV, the inhibition rate of MERS-CoV increased (5). In another MERS-CoV and SARS-CoV cell cultures treated with BCX4430 for 18 hours, the same results have obtained that means by increasing the drug concentration, the inhibition rate of the viruses increased. Moreover, in SARS-CoV culture, by administrating 2 micM of the drug, the inhibition rate became approximately 90% (9). Therefore, adding Galidesivir to the SARS-CoV-2 cell culture may stop its proliferation. Also, clinical trials have shown that this drug is safe and well-tolerated in both IM or IV injection and oral routes (5).

A molecular docking study showed the effect of Galidesivir on inhibiting RdRp, by modeling, validating, and targeting with Galidesivir and different anti-polymerase drugs currently available in the market approved for use against various RNA viruses (2). RdRp modeled from

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SARS-CoV RdRp because the study showed that much of the SARS-CoV-2 RdRp sequence was very similar to other coronaviruses (60.9- 98.1%). Moreover, this sequence was also most similar to the SARS-CoV-2 type compared to other Coronaviruses (98.1%) (10). Galidesivir attached to the RdRp by four hydrophobic and six hydrophilic bonds with comparable binding energies to the main nucleotide ligands, which demonstrated that the drug could bind tightly to the catalytic center of SARS-CoV-2 RdRp (2, 10). Another study showed that among 37 compounds that were considered as candidates for attaching to the virus, Galidesivir interacts with more than two protein structures of SARS-CoV-2. These protein structures include SARS-CoV-2 main proteases with co-crystallized structure (PDB ID 5R7Y, 5R7Z, 5R80, 5R81 and 5R82) (11).

As a result, we conclude that Galidesivir can attach tightly to the catalytic center of RdRp and some other structural proteins of SARS-CoV-2 and inhibit the replication of the virus so it can be considered as a useful treatment for new coronavirus disease. However, until now, only one clinical study has been performed to examine the efficacy of this drug. The mentioned study is currently ongoing to evaluate the pharmacokinetics, safety, and antiviral activity of Galidesivir in hospitalized adult patients with either Yellow Fever or COVID-19. In part 1 of this phase 1 clinical trial, different doses of Galidesivir or placebo are administered every 12 hours in three groups of patients for 7 days. The favorable dosing regimen of Galidesivir is considered for part 2 based on parameters such as safety, pharmacokinetics, viral load reduction, improvement in clinical manifestations, and mortality. In part 2, new eligible patients are treated with an optimized dose of Galidesivir or placebo (12). Altogether, it is recommended to perform more randomized controlled clinical trials to evaluate the effectiveness of the drug in patients with COVID-19.

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