

Commentary

Remdesivir may not be a miracle as expected in anti-COVID-19 therapy

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ABSTRACT

As of January 22, 2020, a total of 571 cases of the COVID-19 coronavirus have been reported in 25 provinces (districts and cities) in China and the coronavirus has spread out in many countries and endangers thousands of lives, worldwide since its outbreak in China. It causes respiratory illness in people but at present, there are no medicines or specific treatment for the disease. Two anti-HIV protease inhibitors, lopinavir, and ritonavir are recommended for the treatment of the disease and a hospital in Wuhan has started a clinical trial using a combination of two drugs that had been tested on MERS patients in Saudi Arabia. The pandemic has also speeded up the development of novel coronavirus vaccines by pharmaceutical companies and research organizations in the United States. Traditional Chinese Medicines are also among the various options for the treatment of the disease like Chloroquine that is an anti-malaria medicine (Am J Transl Med 2020. 4:70-74).

Keywords: 2019-nCoV, Chloroquine, HIV, Immunotherapy, protease inhibitor, MERS,
(Manuscript received 6 April 2020, accepted 20 April 2020)

INTRODUCTION

HIV is a well-studied virus and a great number of FDA-approved medicines are recommended for the treatment of HIV infection. The early clinical drugs act

either at the substrate-binding site of the reverse transcriptase, or a non-substrate binding site of the reverse transcriptase, or the viral protease (Casimiro-Garcia et al, 2000). New drugs are continuously developed, acting on the new targets, like fusion inhibitors, CCR5 antagonists, integrase inhibitors,

post-attachment inhibitors, and pharmacokinetic enhancers (Hunter et al, 2005). The majority of available agents are nucleoside/nucleotide analogs. They inhibit the replication of the virus by blocking the synthesis of proviral DNA (Winter et al., 1997). The nucleoside analogs first activated via several phosphorylation steps by cell enzymes to form the corresponding triphosphate nucleotide. The phosphorylated metabolite is the active species that inhibit the reverse transcriptase and viral DNA synthesis. Some analogs can be incorporated into the nucleic acid and terminate the chain growth. Non-nucleoside reverse transcriptase inhibitors are structurally diverse and cripple the reverse transcriptase by binding near to and changing the conformation of the catalytic site. Protease inhibitors inhibit the viral protease at the late stage of the replication cycle.

Due to the panic, people are expecting a miracle cure for Wuhan Coronavirus Disease (Zou, 2020). Urgent need puts Remdesivir on the front lines of fighting the viral infection. Remdesivir directly jumped to Phase III clinical trials against COVID-19 in China. It was developed by Gilead for the treatment of the Ebola virus disease (Holshue et al., 2020). However, it failed the Phase II clinical trials. It belongs to the nucleotide analogs. Their mechanism of action is well studied for the treatment of AIDS. Like anti-HIV analogs, Remdesivir becomes an active species after metabolism (Holshue et al., 2020). The active form confuses viral RNA polymerase and evades proofreading by viral exoribonuclease. It either terminates RNA chains or causes mutations to inhibit viral RNA replication. The only reason to explain such a hurry because Remdesivir was used in the treatment of the first patient with COVID-19 infection in the United States (Sheahan and Sims, 2017). the first case of COVID-19 pneumonia in the United States, After the treatment, his medical condition improved. However, this is the only case and the possibility of self-healing cannot be completely ruled

out. Furthermore, many anti-HIV drugs are belonging to the same category (nucleoside/nucleotide analogs). They have similar structures and similar mechanisms of action against RNA virus. Therefore, these current clinical anti-HIV drugs are more worthing trying for the treatment of COVID-19 Coronavirus Disease than Remdesivir.

MECHANISM OF REMDESIVIR IN ANTI- VIRUS THERAPY

Only a few virus-specific events could function as targets for chemotherapeutic intervention. The current clinical drugs act either at the substrate-binding site of the reverse transcriptase (Zidovudine, Didanosine, Zalcitabine,) or a non-substrate the binding site of the reverse transcriptase (Nevirapine and Delavirdine), or the viral protease (Saquinavir, Ritonavir, Indinavir). The majority of available agents are nucleoside analogs. They inhibit the replication of the virus by blocking the synthesis of proviral DNA. The nucleoside analogs first activated via several phosphorylation steps by cell enzymes to form the corresponding triphosphate nucleotide. The phosphorylated metabolite is the active compound that inhibits reverse transcriptase and viral DNA synthesis. Some analogs can be incorporated into the nucleic acid and terminate the chain growth. Non-nucleoside reverse transcriptase inhibitors are structurally diverse and cripple the reverse transcriptase by binding near to and changing the conformation of the catalytic site. Processes that inhibit the viral protease at the late stage of the replication cycles are a large class of clinical drugs, which are mainly used in the treatment of AIDS. Though Remdesivir has been demonstrated in its role in vitro inhibition of replication of the SARS virus, one

of coronavirus (Timothy P. Sheahan et al, 2017), it's inappropriate to blow Remdesivir into a magic medicine for COVID-19 pneumonia recently. In terms of structure, it is a chemically modified nucleotide compound, which has no activity of its own. Only after metabolism can the real active nucleotide part be released in the body, so it is called precursor drug. During the outbreak of Ebola, this small molecule compound (not medicine) was in a hurry to develop and treat Ebola. Phase II of clinical failure (the second phase mainly tests the activity in the human body). Now can we in a hurry to say that it can cure Wuhan pneumonia, and we skip the second stage clinical treatment and do the third stage clinical treatment directly in China. There seem to be two reasons for this. First, it is said that the compound is also an RNA reverse transcriptase inhibitor in a mechanism. Both the Ebola virus and the COVID-19 virus are RNA viruses. We would state that the statement is untenable because Ebola failed in the last attempt. In our speculation, the probability of success is small. Second, it was used in the first case of COVID-19 pneumonia in the United States and the disease improved the next day. It's just an isolated case and it's hard to explain and exclude self-healing of viral infection. We noticed that the patient started taking the medicine on the seventh day. Judging from the cold, it began to recover in a week or so. The possibility of self-healing is not ruled out.

Both the SARS virus and the COVID-19 virus use the same receptor protein ACE2 to invade host cells, which does not mean that all the drugs of SARS can be used for COVID-19 pneumonia. More than 700 cases have been cured in China, and 1 case has been cured in the United States (out of 11). Hope depends on China itself.

REMDESIVIR IN TREATMENT

OF COVID-19 INFECTION

It is too far speculating the role of this unproved drug in the treatment of COVID-19 infection and pneumonia. During the discussion of that paper in NEJM, the authors pointed out that on the 4th and 7th day of this patient's illness (not hospitalization), the virus has a high load level and therefore has the potential for transmission. It is also worth noting that the stool is positive for the new coronavirus. We don't know much about the potential effects outside the respiratory tract judging from this case, the Patient only had fever and cough in the early stage, and the disease did not progress to the stage of pneumonia until the ninth day of symptoms. Considering that the early symptoms are very mild and similar to other winter infectious diseases, this also increases the difficulty of diagnosis. Regarding the treatment of Remdesivir, the authors believe that this is based on the patient's worsening condition. Treatment using at the US "compassionate use" principle. Although this patient's condition showed rapid remission after treatment, we still need to conduct randomized controlled clinical trials to determine the safety and effectiveness of Remdesivir and other research drugs in the treatment of new coronavirus infections. We also expect that more clinical data can be published, guide clinical treatment with successful clinical cases, and free patients from the suffering of disease as soon as possible.

IS IT APPROPRIATE TO TRY RAMDESIVIR THERAPY IN COVID-19 INFECTION UNDER COMPASSINATE USE?

We would state it is abused to apply Remdesivir in COVID-19 infection using Compassionate use. First, most of the patient of COVID-19 infection happened in Wuhan, China, this is a non-IND pre-drug which has less than 10 patients currently in the USA, however, it has over 10000 patients in China. There were more cases with COVID-19 infection has been cured in pathogen examination in PCR in the medical laboratory for two times in the patients in Wuhan and most patients did not take Remdesivir.

Consequently, the paper published in NEJM about the case may influence the stock market of this drug and may give wrong information to the investor which is unfair. Furthermore, there is no Compassionate Use policy for an unproven drug in China currently. It may be reasonable to recommend FDA approved drugs in other Coronavirus therapy, if existing, to test the therapy of this novel COVID-19. But not this Remdesivir, The Wall Street Journal, a business journal, already published a commercial article named "Gilead Sciences Offers Experimental Drug for Coronavirus Treatments, Testing."

In sum, it is not rigorous that NEJM to publish such a Remdesivir relevant paper by Compassionate Use mechanism, which may bring the conflict of interest in the pharmacy industry and misconduct the cluster patients of COVID-19 infection in this outbreak in Wuhan, China, and china's physicians in fighting against this COVID-19 outbreak

IS THERE ANY OTHER CANDIDATE DRUGS FOR THE TREATMENT OF COVID-19 INFECTION?

The Jin Yintan Hospital in Wuhan, China, where the first 41 known patients were treated, has already launched a randomized, controlled trial of the anti-HIV drug combination of lopinavir and ritonavir, according to a 24 January report by a group of Chinese scientists in The Lancet, a medical journal published in England. The combination targets protease, an enzyme used by both HIV and coronaviruses to cut up proteins when they make new copies of themselves worldwide, there is an urgent need to treat the disease. However, there is no approved medicine for the treatment. Anti-HIV drugs have been proposed to target the disease due to a similar mechanism of action. Both COVID-19 and HIV are RNA viruses using RNA rather than DNA as genetic material. With the assistance of viral reverse transcriptase, viral RNA is covered to double-strand DNA. Anti-HIV drugs target the viral reverse transcriptase as DNA chain terminators. Anti-HIV drugs also can target viral protease to prevent viral replication. Therefore, it is reasonable to use them to treat the COVID-19 while waiting for a new miracle appearance. The Chinese government suggested that people infected with the coronavirus should take two protease inhibitors lopinavir/ritonavir and inhale interferon twice a day. Other anti-HIV drugs targeting reverse transcriptase also worth trying. Remdesivir was originally developed by Gilead to treat Ebola that failed the clinical trials II due to low efficiency. Although the lab test shows it is effective to COVID-19, there is even no test on animals. However, this unproved agent was administrated to a patient by making a "compassionate use."

IMMUNOTHERAPY

Besides, Immunotherapy, such as NK cell therapy or antigen-specific CTL cell therapy may be better than Remdesivir therapy in this regard in clinical "trial" in the base of Compassionate Use in China where there

are more than two thousand patients. Which may bring better effort in therapy compare to Remdesivir in our speculation. Unfortunately, this Cell immunotherapy against the new coronavirus has yet been recommended at all currently. But, presently the ImmunoPrecise's approach involves various mechanisms of the immunity and proficient to predict mutations of the virus genome, along with different characteristics for a maximum clinical benefit against existing and future strains. Besides, we suggest NK cell therapy may be also a considerable option for the treatment of this disease.

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