EDITORIAL NOTES

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.pharmascope.org/ijrps

VYTR hypothesis for the prophylactic and therapeutic efficacy of GS-5734 treatment in humans with COVID-19

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Article History:

Received on: 20 Feb 2020
Revised on: 26 Mar 2020
Accepted on: 28 Mar 2020

Keywords:

Remdesivir,
GS-5734,
VITYALA YETHINDRA (VYTR) hypothesis,
SARS-CoV-2,
COVID-19,
Therapeutic treatment,
Prophylactic treatment

ABSTRACT

In December 2019, many pneumonia cases were reported without an apparent cause but were associated with seafood and wet markets in Wuhan, China Clinical features were similar to pneumonia, and SARS- CoV-2 (formerly 2019-nCoV) was determined as the causative pathogen. To date, there are no effective antiviral drugs for the targeted treatment of coronavirus disease 2019 (COVID-19). We provide the VITYALA YETHINDRA (VYTR) hypothesis for the prophylactic and therapeutic efficacy of GS-5734 treatment in humans with COVID-19. Prophylactic GS-5734 treatment may prevent SARS-CoV-2 induced disease and lung lesions in participants inoculated with SARS-CoV-2 and potentially inhibit SARS-CoV-2 replication. Therapeutic GS-5734 treatment may show a reduction in the severity of symptoms, reduce viral replication, the complete eradication of lung lesions in some participants and decrease in the extent of lesions in 50% of participants may be possible. As broad-spectrum drugs are capable of inhibiting coronavirus infections, GS-5734 should be considered a broad-spectrum, first-line drug and may inhibit coronavirus infections and COVID-19. More clinical trials are needed to prove that GS-5734 (Remdesivir) is a safe and effective drug for the treatment of COVID-19.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11iSPL1.2007

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INTRODUCTION

In December 2019, many pneumonia cases were reported without an apparent cause but were associated with seafood and wet markets in Wuhan, China (Wuhan Municipal Health Commission, 2019). Clinical features were similar to pneumonia, and SARS- CoV-2 (formerly 2019-nCoV) was determined as the causative pathogen. To date, there are no effective antiviral drugs for the targeted treatment of coronavirus disease 2019 (COVID-19). GS-5734 (Remdesivir) is a nucleotide prodrug with broad antiviral activity (Lo *et al.*, 2006). GS-5734 inhibits SARS-CoV and MERS-CoV in HAE cells during the

early stages of replication, and the absence of exon-mediated proofreading in viruses may explain the sensitivity to treatment with GS-5734 (Yethindra, 2020). In mice, GS-5734 showed therapeutic efficacy against SARS-CoV and MERS-CoV if administered before the peak of viral replication (Sheahan *et al.*, 2017; Agostini *et al.*, 2018). We provide the VITYALA YETHINDRA (VYTR) hypothesis for the prophylactic and therapeutic efficacy of GS-5734 treatment in humans with COVID-19.

VYTR hypothesis

Increased concentrations of GS-5734 may show a consequent reduction in the viral titre for SARS-CoV-2 (Yethindra, 2020). Specifically, delaying the GS-5734 treatment from 24 h – 48 h post-infection may show reduced viral titre for SARS-CoV-2, as increased concentrations of GS-5734 may reduce the levels of viral RNA associated with titre reduction (Yethindra, 2020). GS-5734 may inhibit SARS-CoV-2 during the early stages of replication by inhibiting viral RNA synthesis (Yethindra, 2020). Prophylactic GS-5734 treatment may prevent SARS-CoV-2 induced disease and lung lesions in participants inoculated with SARS-CoV-2 and potentially inhibit SARS-CoV-2 replication. Therapeutic GS-5734 treatment may show a reduction in the severity of symptoms, reduce viral replication, the complete eradication of lung lesions in some participants and decrease in the extent of lesions in 50% of participants may be possible.

GS-5734 may relieve symptoms after prophylactic and therapeutic treatment

To evaluate the effectiveness of GS-5734 to relieve symptoms of SARS-CoV-2, participants should be divided into two groups. The first group of participants should be prophylactically treated 24 h before SARS-CoV-2 inoculation with GS-5734. The second group of participants should be therapeutically treated at 12 h post-inoculation, also with GS-5734. Treatment should be continued once per day for 6 days post inoculation (dpi). On day 0, all participants may show symptoms, and clinical scores should be evaluated by formally regulated scoring data. Prophylactically treated participants with GS-5734 may not show respiratory signs, but in many participants, there may be reduced appetite and somnolence because anesthesia is to be performed every day. In therapeutically treated participants with GS-5734, all participants may display decreased appetites, and show elevated respiration rates. At 1 dpi, in therapeutically treated participants respiration rate may be elevated, at 3 and 6 dpi respiration rate may then be depressed (Table 1). At 2 to 4 dpi, prophylactically treated participants will likely report clinical scores that are lower than those of therapeutically treated participants. In prophylactically treated participants, respiration rates will be normal. At 3 dpi, on radiography, lung infiltrates will be observed. At 6 dpi, there will be less lung infiltrates when treated both prophylactically and therapeutically with GS-5734.

Viral load in the lungs will decrease in GS-5734 treated participants

Prophylactic GS-5734 treatment results in lower levels of SARS-CoV-2 replication within the lungs and lowered lung viral loads. Therapeutic GS-5734 treatment results, lung viral loads will be lower in lung lobes but seen in only a few lung lobes. If all lung lobes were integrated, in therapeutically treated participants, lung viral loads will be low. In prophylactic and therapeutic treated participants, viral loads will be low in the trachea, bronchi, and lymph nodes (mediastinal) and there will be no evidence of viral RNA in kidney tissue samples.

Decreased severity of gross and histologic lung lesions upon treatment with GS-5734

Gross lung lesions should be totally absent in the lungs of participants who received prophylactic GS-5734 treatment. Gross lung lesions may still be present in many participants who received treatment therapeutically with GS-5734; however, the severity of histologically examined lung lesions will be evaluated by evaluating a score for each lung lobe. In prophylactically treated participants with GS-5734, cumulative lung histology scores are expected to be significantly lower (Table 2). If participants are therapeutically treated, cumulative lung histology scores should be significantly higher (Table 2). Histologically, all participants are expected to develop some degree of lung pathology if inoculated with SARS-CoV-2. In participants, multifocal lesions will be centered on terminal bronchioles, and minimal-to-moderate interstitial pneumonia will likely manifest, alveolar septae will be thickened by oedema, fluid and minimal-to-moderate numbers of macrophages and neutrophils will be observed. The lesions will be reduced and will unlikely be widely distributed throughout the lung lobes. Participants treated with GS-5734 prophylactically should have normal lung tissue with no signs of infection. Participants treated therapeutically will likely present with greater viral pneumonia severity. In many therapeutically treated participants, fewer pneumocytes (antigen-positive type I) and SARS-CoV-2 antigen levels will be detected (Table 2). In prophylactically treated participants, the SARS-CoV-2 antigen may not be detected at all (Table 2).

Table 1: Respiration rates in prophylactically and therapeutically treated participants

Therapeutically treated participants	
days post inoculation (dpi)	Respiration rate
1 dpi	Elevated
3 and 6 dpi	Depressed
Prophylactically treated participants	
1-6 dpi	Normal

Table 2: Comparison of Cumulative lung histology scores and detection of SARS-CoV-2 antigen levels in prophylactically and therapeutically treated participants.

Treatment	Cumulative lung histology scores
Prophylactic	Low
Therapeutic	High
	SARS-CoV-2 antigen levels
Prophylactic	Not detected
Therapeutic	Detected

Five postulates of VYTR hypothesis,

1. Increased concentrations of GS-5734 may show a consequent reduction in the viral titre for SARS-CoV.

2. Specifically, delaying the GS-5734 treatment from 24 h – 48 h post-infection may show reduced viral titre for SARS-CoV-2.

3. GS-5734 may inhibit SARS-CoV-2 during the early stages of replication by inhibiting viral RNA synthesis.

4. Prophylactic GS-5734 treatment may prevent SARS-CoV-2 induced disease.

5. Therapeutic GS-5734 treatment may show a reduction in the severity of symptoms that reduce viral replication.

CONCLUSIONS

Viral diseases can be catastrophic like COVID-19, and they may have both social and economic issues. Strict, well-organized, structured, and scheduled infection control policies should be made national and international wide. To prevent outbreaks, hospitals should be ready with control measures and protocols during handling cases. As broad-spectrum drugs are capable of inhibiting corona virus infections, GS-5734 should be considered a broad-spectrum, first-line drug and may inhibit corona virus infections and COVID-19. More clinical trials are needed to prove that GS-5734 (Remdesivir) is a safe and effective drug for the treatment of COVID-19.

Conflict of interest

The authors declare no conflict of interest.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical Considerations

Compliance with ethical guidelines

There is no ethical principle to be considered during this research.

ACKNOWLEDGEMENT

I was an undergraduate student. I am proud and lucky to conduct research and propose a hypothesis. As Vityala Yethindra, I am very thankful to my parents Vityala Anitha, Vityala Thirupathi, and my sister Vityala Srilaxmi, for their valuable support in continuing research. I wish to thank, Dr. Cholpon Dzhumakova, Dr. Elmira Mainazarova, Dr. Mamatov Sagynali Murzaevich, Panchadcharam Harinath, and Dr. Melis Sholpanbai Uulu for their help in carrying out research and useful criticisms of this manuscript. I am highly disheartened with the deaths of people, and our article is only a drop in the ocean, and more findings are yet to come. This article is dedicated people who died with SARS-CoV-2, and my inspiration late Dr. Liang Wudong and Dr. Li Wenliang, doctors, and scientists.

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