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

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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). 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

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 exo-
mediated proofreading in viruses may explain the
sensitivity to treatment with GS-5734 (Yethindra,
2020). In mice, GS-5734 showed therapeutic effi-
cacy against SARS-CoV and MERS-CoV if adminis-
tered before the peak of viral replication (Shea-
han et al., 2017; Agostini et al., 2018). We pro-
vide 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 reduc-
tion (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 partici-
pants inoculated with SARS-CoV-2 and potentially
inhibit SARS-CoV-2 replication. Therapeutic GS-
5734 treatment may show a reduction in the sever-
ity of symptoms, reduce viral replication, the com-
plete eradication of lung lesions in some partici-
pants and decrease in the extent of lesions in 50%
of participants may be possible.

GS-5734 may relieve symptoms after prophylac-
tic 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 par-
ticipants should be prophylactically treated 24 h
before SARS-CoV-2 inoculation with GS-5734. The
second group of participants should be therapeu-
tically 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 per-
formed every day. In therapeutically treated par-
ticipants with GS-5734, all participants may display
decreased appetites, and show elevated respiration
rates. At 1 dpi, in therapeutically treated partici-
pants 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 pro-
phylactically treated participants, respiration rates
will be normal. At 3 dpi, on radiography, lung infil-
trates 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 evi-
dence 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 treat-
ment 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, cumula-
tive 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 bronchi-
oles, and minimal-to-moderate interstitial pneumo-
nia will likely manifest, alveolar septae will be thick-
ened 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 prophy-
lactically should have normal lung tissue with no
signs of infection. Participants treated therapeuti-
cally will likely present with greater viral pneumo-
nia severity. In many therapeutically treated par-
ticipants, 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

| days post inoculation (dpi) | Therapeutically treated participants | Respiration rate |
|-----------------------------|-------------------------------------|-----------------|
| 1 dpi                       | Elevated                            |                 |
| 3 and 6 dpi                 | Elevated                            |                 |
| Prophylactically treated    | Normal                              |                 |
| 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 | SARS-CoV-2 antigen levels |
|----------------------------|---------------------------------|--------------------------|
| Prophylactic               | Low                             | Not detected             |
| Therapeutic                | High                            | Detected                 |
| Prophylactic               | Low                             | Not detected             |
| Therapeutic                | High                            | 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.

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