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RESEARCH ARTICLE

Status of Antiviral Agents in Treatment of COVID-19

Savita R. Shahani[1], Lokesh R. Shahani[2]

[1]MGM Medical College, Navi Mumbai, Maharashtra, India, [2]McGovern Medical School, Houston, Texas, United States

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ABSTRACT

Severe acute respiratory syndrome coronavirus-2 is responsible for COVID-19, a novel disease which was first identified in city of Wuhan in China. The World Health Organization declared official name of the disease as COVID-19. Due to presence of spike glycoproteins on its envelope, it was named as a coronavirus. Promising drug targets for anti-COVID activity include non-structural proteins such as 3-chymotrypsin-like protease, papain-like protease, and RNA-dependent RNA polymerase. Additional drug target includes viral entry. Various drugs which are tested for COVID-19 infection are described here with their present status: (1) Lopinavir–ritonavir-Both the drugs are protease inhibitors and are given as combination therapy currently none of the guidelines recommend Lopinavir–ritonavir for the treatment of COVID-19, as clinical trials have not demonstrated its benefit in COVID-19. (2) Favipiravir (FPV)-It is a broad-spectrum antiviral drug which acts by inhibiting viral RNA-dependent RNA polymerase. None of the organizational guidelines recommend using FPV in the management of COVID-19, due to varying results of existing clinical trials data. (3) Remipiravir (REM)-It is also a broad-spectrum antiviral drug which acts by inhibiting viral RNA-dependent RNA polymerase. United States Food and Drug Administration has approved the REM for the treatment of COVID-19 in adults and children above 12 years in hospitalized COVID-19 patient. Drug Controller General of India has granted approval to REM for restricted emergency use for the treatment of COVID-19 but guidelines for the management of COVID-19 among children issued by the government of India mentions that there are insufficient data regarding safety and efficacy of REM in children below 18 years of age. The WHO has issued a conditional recommendation against the use of REM in hospitalized patients, regardless of disease severity, due to insufficient evidence that REM improves survival and other outcomes in these patients. Some of the newer antiviral drugs are in various phases of clinical trials for the treatment of COVID-19. How these potential COVID-19 treatments will translate to effective therapy in human is difficult to predict.

Keywords: Favipiravir, lopinavir–ritonavir, remipiravir, severe acute respiratory syndrome coronavirus-2

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a previously unknown pathogen, is responsible for COVID-19 a novel disease which was first identified in city of Wuhan in Central China. The name SARS-CoV-2 was given by International Committee on Taxonomy of Viruses and World Health Organization (WHO) declared official name of the disease as COVID-19. Due to presence of spike glycoproteins on its envelope, it was named as a coronavirus.[1]

Viruses are obligatory intracellular microorganisms which rely on host's biosynthetic machinery for multiplication. Effective antiviral agents preferentially inhibit virus-directed rather than host cell-directed nucleic acid or protein synthesis. Host

***Corresponding Author:**
Savita R. Shahani,
E-mail: drshahani@rediffmail.com

cell molecules that are essential to viral replication also offer targets for intervention. SARS-CoV-2, a single-stranded RNA-enveloped virus, targets cells through the viral structural spike(S) protein that binds to the angiotensin-converting enzyme 2 receptor. Following receptor binding, the virus particle enters into host cells. Once inside the cell, virus then synthesizes RNA through its RNA-dependent RNA polymerase (RdRp) and other structural proteins are synthesized leading to completion of assembly and release of viral particles.[2]

Promising drug targets for anti-COVID activity include non-structural proteins (3-chymotrypsin-like protease [3CLpro], papain-like protease [PLpro], and RdRp). Additional drug target includes viral entry. Viral replication is particularly active early in the course of COVID-19; therefore, antiviral therapy may have greatest impact before the illness progresses into hyperinflammatory state. For this reason, understanding the role of antiviral agents in treating disease of various severities is necessary to optimize treatment for COVID-19.

STATUS OF VARIOUS ANTIVIRAL AGENTS IN TREATMENT OF COVID-19

Finding the right treatment for the SARS-CoV-2 continues to be a major challenge. The speed of the normal drug development pathway is unacceptable in context of the present global emergency, but repurposing existing drugs and genomic sequencing of COVID-19 has facilitated this process.[3] Various drugs which are tested for COVID-19 infection are described here with their present status.

Lopinavir–ritonavir (LPV/r)

LPV/r is the first antiviral agent which was used for the treatment of COVID-19. It was developed for inhibition of HIV protease. As HIV protease has minor difference to 3CLpro of SARS-CoV-2 which justified validity of this medication for the treatment of COVID-19. Lopinavir is a potent inhibitor of 3CLpro coronavirus.[4] Ritonavir is also 3CLpro inhibitor, but its primary role is to prolong half-life of lopinavir through cytochrome P450 inhibition. Earlier studies suggest that early administration of LPV/r is effective in reducing viral load and improving clinical outcomes in patients with mild-to-moderate COVID-19 disease.[5]

A randomized control trial LOTUS China (Lopinavir Trial for Suppression of SARS-Cov-2 in China) was conducted by Cao *et al.* in adult patients hospitalized with COVID-19 at Jin Yin-Tan Hospital, Wuhan, China, which concluded that no benefit was observed in time to clinical improvement and mortality with LPV/r beyond standard care in SARS-CoV-2 infection.[6] After a reviewing the findings of Cao *et al.*, use of LPV/r was discouraged for the treatment of COVID-19. Piero Dalerba *et al.*[7] in letter to editor mentioned that the trial was statistically underpowered to show the outcome. It was suggested that LPV/r may be associated with substantial lowering of overall mortality and risk of respiratory failure. Author suggested that LPV/r should not be abandon for COVID-19, till approved treatment is developed. Osborne *et al.*[8] also concluded that if larger sample size was used, the significant beneficial effect of LPV/r would have been obtained. Various trials being conducted to determine if LPV/r is an effective treatment for COVID-19 are described below.

Recovery (Randomized Evaluation of COVID-19 Therapy) trial was the randomized, controlled, and open-label trial, to compare various treatments (LPV/r, hydroxychloroquine, dexamethasone, and azithromycin) with standard care in hospitalized patients of COVID-19 which was conducted at 176 hospitals in the UK. No significant difference was observed with LPV/r in time of discharge from hospital or number of patients discharged from hospital alive within 28 days compared to standard care.[9] These findings do not support the use of LPV/r for the treatment of COVID-19.

SOLIDARY trial was conducted at 405 hospitals in 30 countries.[10] Results of the study are discussed later. Findings of this study had discouraged off-label use of LPV/r in the present pandemic.

A Phase 2 randomized clinical trial was conducted to establish whether a combination of three modestly active drugs can improve the viral load profile and clinical parameters in adults with

COVID-19 requiring hospital admission from the three hospitals in Hong Kong. The patients having onset of symptom for <7 days received a triple combination of LPV/r and Ribavirin (RdRp inhibitor) with interferon (IFN)-beta-1b, while IFN-beta-1b was omitted in patients treated after 7 days of symptoms, to avoid its proinflammatory effects. The patients assigned to the control group received only LPV/r as placebo was not accepted in China. In patients having prolonged QTc or hepatic abnormalality, LPV/r dose was reduced. It was observed that a triple combination, produced significant reductions in duration of viral positivity and viral load in all clinical specimens, compared with LPV/r alone.[11]

A small retrospective data analysis showed that viral load was negative at day 7 post-treatment in 75% of patients with COVID-19 treated with umifenovir (direct-acting antiviral) and LPV/r versus 35% in LPV/r alone.[12] At present, none of the guidelines recommend LPV/r for the treatment of COVID-19 as clinical trials have not demonstrated its benefit in COVID-19.

Favipiravir (FPV)

It is being developed and manufactured by Toyama Chemical (Fujifilm group) during its transition from the photo business to healthcare. FPV is a broad-spectrum antiviral drug which acts by inhibition of viral RdRp.[13] FPV is a prodrug which is metabolized to its active form, FPV-ribofuranosyl-5'-triphosphate (FPV-RTP), and may be misincorporated in a nascent viral RNA, thus preventing incorporation of nucleotides for viral RNA replication and transcription.[14] FPV is known to be teratogenic; therefore, its administration should be avoided during confirmed or suspected pregnancy.[15] The results of various controlled trials to assess the efficacy of FPV for COVID-19 have elucidated the role of FPV in the management of COVID-19.

In a randomized, parallel, multicenter, and Phase 3 trial, COVID-19 patients who were asymptomatic or having mild-to-moderate symptoms (CTRI/2020/05/025114) received FPV plus standard care versus standard care alone. Results suggested that time to cessation of viral shedding was not significantly different in both group, but time to clinical cure was significantly earlier, for FPV suggesting benefit of FVP in mild-to-moderate COVID-19.[16]

The efficacy of FPV versus LPV/r for the treatment of COVID-19 (ChiCTR2000029600) in randomized trials was studied. The patients receiving FPV plus IFN-α were included in the FPV arm, whereas in control arm patients received LPV/r plus IFN-α. FPV showed better therapeutic responses in COVID-19 in terms of reduction in disease progression and viral clearance.[17]

A three arms exploratory trial was conducted in hospitalized adult patients with COVID-19. The patients were randomly assigned into baloxavir marboxil, FPV, and control group. The primary outcome was the percentage of viral negative subjects by day 14, time to clinical improvement and virus load reduction (ChiCTR 2000029544).[18] Study findings do not support any benefit of either baloxavir or FPV to the standard treatment.

In the United States, a Phase 2 trial (NCT04358549) with COVID-19, in collaboration with Brigham and Women's Hospital and Massachusetts General Hospital, is being conducted. Results of this trial are not declared. In a prospective, randomized, and multicenter study (ChiCTR2000030254), FPV was compared with umifenovir for the treatment of moderate and severe COVID-19 infections. No significant differences were observed in clinical recovery at day 7, even though FPV significantly improved clinical symptoms earlier.[19]

The preliminary report on FPV observational registry from Japan in COVID-19 cases reported that the rate of clinical improvement at day 7 and 14 from the start of FPV therapy improvement was better in mild case compared to moderate and severe case. However, the clinical improvement among subgroup of patients with <60 years of age was better.[20]

A prospective, randomized, and open-label trial of early versus late FPV treatment in hospitalized patients with COVID-19 conducted at 25 hospitals across Japan showed a trend toward better viral clearance and faster defervescence in the early treatment group.[21]

In India, FPV was accepted by the Drug Controller General of India (DCGI) for "restricted emergency use to treat patients with mild-to-moderate COVID-19 disease on June 19 but newer guidelines issued by Director General for Health Services have dropped FPV from its treatment guideline.[22] However, none of the organizational guidelines include Infectious Diseases Society of America (IDSA) guidelines, WHO guidelines, and National Institutes of Health guidelines recommend using FPV in the management of COVID-19, given the varying results of existing clinical trials data.

Remipiravir (REM)

REM was originally developed by Gilead Sciences in 2009, as part of the company's research and development program for hepatitis C, subsequently its activity against multiple viruses such as filoviruses, pneumoviruses, paramyxoviruses, and coronaviruses was discovered.[23] REM is a phosphoramidate prodrug of adenosine. It diffuses into cells where it is converted to remdesivir monophosphate through the actions of esterases; which is further phosphorylated to its active metabolite remdesivir RTP by nucleoside-phosphate kinases. RTP delays RNA chain termination and destabilizing the complex thus reducing the complex's ability to bind to RNA, leading to reduced replication efficiency of virus. While studying interaction of REM, ribavirin, and FVP, on RdRp complex of SARS-CoV-2, it was observed that REM binds to nucleotide binding site more effectively than other two drugs.[24]

On January 21, 2020, the Wuhan Institute of Virology applied for a Chinese "use patent" of REM for treating COVID-19. On June 2020, the United States Food and Drug Administration (USFDA) warned against coadministration of REM and chloroquine or hydroxychloroquine as data suggested an antagonistic effect of chloroquine on the intracellular activation and therefore antiviral activity of REM.[25]

The first case report of REM use in COVID-19 originated from the United States. A 35-year-old gentleman was admitted for monitoring for COVID like symptoms. REM was administered as a trial drug to him. Within 2 days of the treatment, the patient showed clinical improvement.[26] Another case report also mentioned patient's recovery after REM use.[27] Although both studies regarding REM as potential candidate for COVID-19 therapy were limited to case reports. Subsequently, in small cohort, REM was administered on a compassionate use basis to hospitalized COVID-19 patient. Data were analyzed for 22 patients from United States, 22 from Europe or Canada, and 9 from Japan. It was observed that 68% had improvement in oxygen-support including 57% receiving mechanical ventilation were extubated. A total of 47% patients were discharged, with mortality of 18% among patients receiving invasive ventilation and 5% among those not receiving invasive ventilation.[28] Subsequent prospective studies on compassionate use of REM suggested improvement in oxygen requirement, ability to wean of ventilatory support, and improved clinical outcomes.[29] Both these studies had limitation of small sample size and absence of a comparator group.

The first randomized double-blinded and placebo controlled multicenter trial was conducted by Wang *et al.* in Hubei, China, where the patients received REM or placebo. Time to clinical improvement within 28 days, though not significant, was shorter in the REM treated group compared to control group. No significant differences were observed in mortality, duration of oxygen requirement, length of hospital stay, and viral load in both groups. This study remained inconclusive as target enrollment could not be achieved, due to declining incidence of COVID-19 in China, causing poor statistical power. Although not statistically significant, patients with COVID-19 who received REM clinically improved faster than placebo arm.[30]

The Adaptive COVID-19 Treatment Trial (ACTT) which was sponsored by the National Institute of Allergy and Infectious Diseases was the first clinical trial launched in the United States to evaluate an experimental treatment for COVID-19. Adaptive trial of REM (NCT04280705) was started first against placebo, but additional therapies were added to the protocol as evidence emerged. ACTT-1 trial was conducted at multiple sites in the United States (45), Denmark (eight), the

United Kingdom (five), Greece (four), Germany (three), Korea (two), Mexico (two), Spain (two), Japan (one), and Singapore (one). The first trial participant in the ACTT trial was an American who after returning to the United States from Japan was being quarantined on the Diamond Princess cruise that docked in Yokohama, Japan. The patients randomly received REM or placebo for 10 days. Results showed that REM shortened recovery time even though the mortality was not considered here. In this trial, the subset of patients requiring oxygen supplementation but not high-flow oxygen or ventilatory support, REM had a significant mortality benefit. Although credibility of this subgroup analysis is questionable, results suggest that this finding may not be bychance. For individuals at high risk of hyperinflammation who were diagnosed early during illness (≤10 days) and require supplemental oxygen, REM shortened the time to recovery and reduced the risk of disease progression.[31]

The risks and benefits of REM in patients presenting with severe COVID-19 who required high-flow oxygen or mechanical ventilation were uncertain. Virological data from the ACTT-1 trial were not submitted as this was not the aim of study. There was no difference in the decline in viral titers between remdesivir and placebo in the study by Wang *et al*.[30]

Emerging data suggest that disease severity may be due in part to a dysregulated inflammatory response. It is postulated that suppressing the immune response and preventing a hyperinflammatory state may further improve clinical outcomes.[32] Further assessment of the effects of REM on the inflammatory response and virological dynamics would be useful to define role of immunomodulators in critically ill patients. Therefore, effects of combination therapies with REM should be assessed. Even though few trials suggested that the treatment with IFN-beta may benefit patients with COVID-19, but combination of IFN-beta and REM for treating COVID-19 has not been evaluated in a large controlled trials. In China, a combination of IFN-I is being administered with LPV/r or REM, which could increase the efficiency of the treatment against COVID-19.

The UK-based RECOVERY trial which is discussed earlier[9] showed that dexamethasone administration led to a significant reduction in mortality rate which led to corticosteroids being considered with standard of care. Whether there is an additional benefit from using both REM and corticosteroids and requires further evaluation.

Therefore, a retrospective comparative effectiveness research study was conducted in five hospitals in the USA in COVID-19 patients. The patients who received REM were matched to individuals who did not receive REM using time invariant covariates (age, sex, race/ethnicity, comorbidity index, body mass index, and do-not-resuscitate or do-not-intubate orders) and time-dependent covariates (ratio of blood oxygen saturation to fraction of inspired oxygen, blood pressure, pulse, temperature, respiratory rate, and laboratory parameters). REM recipients had a shorter time to clinical improvement and reduced 28-day mortality rate than matched controls without REM treatment, but this difference was not statistically significant in the time-to-death analysis. The addition of corticosteroids to REM was not associated with a reduced hazard of death at 28 days.[33]

As adaptive trial was designed to incorporate additional investigational treatments, second iteration of the ACTT, ACTT 2, was to evaluate the safety and efficacy of REM and anti-inflammatory drug baricitinib for treating hospitalized adults with COVID-19 at 71 various international sites. Baricitinib plus REM was superior to REM alone in reducing recovery time and accelerating improvement in clinical status among patients with COVID-19, especially among those receiving high-flow oxygen or non-invasive ventilation.[34] Although ACTT-2 was not powered to detect a difference in mortality between two groups, both survival rate and the time-to-death analyzes favored combination treatment.

ACTT 3 (NCT04492475), which was a randomized and controlled clinical trial evaluating the safety and efficacy of a treatment regimen consisting of the antiviral REM plus immunomodulator IFN-beta-1a in patients with COVID-19, has begun. The study anticipated to enroll more than 1000

hospitalized adults with COVID-19 at around 100 sites in the United States and other countries. ACTT 3 participants were being randomly assigned to receive either IFN-beta-1a plus REM or REM alone to evaluate whether time to recovery is shorter in the combination therapy group compared to the REM only group. Study results are awaited yet.

Fourth iteration of the ACTT 4 study was conducted to evaluate the efficacy of combination of baricitinib and REM compared to dexamethasone and REM in hospitalized adults patients of COVID-19. Participants were assessed for their clinical status daily from return to baseline pre-COVID-19 status and not hospitalized up to day 29 or to death. The primary aim of trial was to evaluate the difference in the proportion of participants surviving without requiring invasive mechanical ventilation between the two treatment groups. The trial also aims to compare the overall clinical status at day 15 in each group. An independent data and safety monitoring board evaluating the trial met on March 30, 2021, for interim efficacy analysis. They did not find any significant difference between both treatments.[35]

The global, multicenter, and double-blind REMDACTA study (NCT04409262) was aimed to evaluate the efficacy and safety of tocilizumab in patients with severe COVID-19 pneumonia. The patients were randomly assigned to receive tocilizumab plus REM or REM alone. Results suggested that the treatment with tocilizumab plus remdesivir did not meet the primary end point of improvement in time to hospital discharge by day 28 or secondary end points such as likelihood of death, progression to mechanical ventilation or death, and clinical status.[36]

SOLIDARITY trial[10] was conducted using various study drugs which were REM, hydroxychloroquine, LVP/r, and IFN-β-1a. COVID-19 inpatients were randomized to whichever study drugs were locally available and control (up to five options: four active and local standard care). On analysis of data, it was observed that no study drug definitely reduced mortality, initiation of ventilation, or hospitalization duration, concluding that for patients with COVID-19 who do not require respiratory support, REM does not offer significant benefit at day 28 and its use is not recommended. One limitation of this study is the lack of data on the duration of symptoms before the initiation of remdesivir. Since REM is likely to be beneficial in the early viral replication phase rather than the inflammatory phase before dysregulated host immune response had started. These findings, therefore, should not be interpreted that remdesivir has no role in the treatment of COVID-19.

Gilead initiated two randomized Phase 3 clinical trials SIMPLE studies, in countries with a high prevalence of COVID-19 infections. First study was a randomized and open-labeled Phase 3 (SIMPLE-Severe trial) which was conducted in multiple countries to evaluate the safety and efficacy of different dosing regimens of remdesivir (5 days vs. 10 days) in patients with severe COVID-19. Post hoc analysis did not demonstrate any improved outcomes with REM treatment beyond 5 days in patients who were receiving non-invasive ventilation, any supplemental oxygen, or breathing ambient air. In multivariate analysis, duration of clinical improvement was better in patients with <65 years of age, did not require supplemental oxygen, or only required low flow oxygen and not on any biologic treatment. Efficacy of REM cannot be determined in this study as it lacked a placebo arm.[37] Although there was a trend toward better outcomes in the group treated with REfor 5 days. Limitation of study was that 10-day remdesivir treatment group included a significantly higher proportion of patients with more severe COVID-19 disease, requiring invasive mechanical ventilation and high-flow oxygen.

Second trial Gilead Sciences initiated was the Phase 3 SIMPLE trial (SIMPLE-moderate) of REM in hospitalized patients with moderate COVID-19 pneumonia to assess 5-day and 10-day courses of the drug in combination with standard care, compared to standard care alone with primary end point on clinical status. On day 11, the patients in the 5-day REM group had significantly better clinical status than those receiving standard care but clinical status between the 10-day REM and standard care groups was not significantly different concluding that the patients with moderate COVID-19 disease may also benefit from a 5-day treatment course of remdesivir.[38] As transaminase

elevation was observed in patients with COVID-19 in clinical trials who received REM, monitoring renal, and hepatic function before initiating and daily during therapy is required.

REM shortens time to recovery in adults with severe COVID-19, but its efficacy and safety in children were unknown. Therefore, outcome in children with severe COVID-19 treated with REM was studied among 77 children. The most of children treated with REM recovered, with three deaths which were attributed to COVID-19. The rate of serious adverse events was low. Among laboratory abnormalities, elevation in transaminase levels was common.[39]

These results prompted USFDA to grant Emergency Use Authorization (EUA) of REM for patients with severe COVID-19, on May 1, 2020, but in other cases, its safety is not been established. In October 2020, the USFDA approved the antiviral drug REM to treat COVID-19 to treat adults and children above 12 years, who have been hospitalized for COVID-19. DCGI has approved REM restricted emergency use for the treatment of COVID-19 on July 2020. On November 20, 2020, the WHO issued a conditional recommendation against the use of REM in hospitalized patients, regardless of disease severity, as there is currently no evidence that REM improves survival and other outcomes in these patients. Second version of a guidelines document by the Scientific Medical Policy Committee of the American College of Physicians based on an updated systematic review recommended use of remdesivir in the treatment of COVID-19, but mentioned that there is insufficient evidence to consider the use of REM in patients who do not require supplemental oxygen at the time of drug initiation. IDSA panel recommends use of REM over no antiviral treatment in hospitalized patients with severe COVID-19. In patients on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with 5 days of remdesivir rather than 10 days of REM.

Comprehensive guidelines for the management of COVID-19 among children have been issued by the Government of India which mentions that there are insufficient data regarding safety and efficacy of REM in children below 18 years of age; therefore, REM is not recommended.[40]

Outcomes in the first 86 pregnant women who were treated with REM found high recovery rates and no new safety signals were observed.[41] A Phase 1b trial of an inhaled nebulized version was initiated in late June 2020 to determine if remdesivir can be used on an outpatient basis and at earlier stages of disease. Delivering remdesivir directly to the primary site of infection with a nebulized, inhaled solution may enable more targeted and accessible administration in non-hospitalized patients and potentially lower systemic exposure to the drug,[42] Other upcoming antiviral agents which are being tested for COVID-19 are discussed below.

Galidesivir (Gali)

Gali is an adenosine analog antiviral drug. It is developed by BioCryst Pharmaceuticals, intended as a treatment for hepatitis C, but subsequently tried as a potential treatment for deadly coronavirus. Gali binds to viral RNA polymerase, leading to the structural change in the viral enzyme causing disruption of viral RNA polymerase activity producing premature termination of the elongation of RNA strand.[43]

Phase 1 human trial of Gali is conducted for coronavirus at Brazil under a U.S. investigational new drug application. Part 1 of the study was conducted in hospitalized patients with moderate-to-severe COVID-19. The patients were randomized to receive Gali in three dosing regimens of 10 mg/kg then 2 mg/kg (Cohort 1), 10 mg/kg then 5 mg/kg (Cohort 2), 20 mg/kg then 5 mg/kg (Cohort 3), or placebo every 12 h for 7 days. The study showed that all three dose levels were equally safe. Gali treatment was associated with a more rapid decline in viral RNA levels in the respiratory tract in dose-dependent manner.[44]

Pfizer's investigational agents

Pfizer has initiated a study of an investigational antiviral agent, PF-07321332, to study its efficacy in COVID-19. This agent is a SARS-CoV2-3CL protease inhibitor showing potent *in vitro* activity

against SARS-CoV-2 and other coronaviruses. Coadministration of PF-07321332 with a low dose of ritonavir is expected to help slow the metabolism, of PF-07321332 so that it remains active in the body for longer periods of time at the higher concentrations to help combat the virus. PF-07321332 was designed as a potential oral therapy that could be prescribed at the first sign of infection or at first awareness of an exposure, without requiring patients to be hospitalized.[45]

Pfizer Inc. has started the Phase 2/3 Evaluation of Protease Inhibition for COVID-19 in Post-exposure Prophylaxis study to evaluate the PF-07321332, coadministered with a low dose of ritonavir, for the prevention of COVID-19 infection. In August, 2021, Pfizer initiated a study to evaluate efficacy and safety in combination with ritonavir, in participants with a confirmed diagnosis of SARS-CoV-2 infection who are at high risk of progression to severe illness (including hospitalization or death) and another in infected patients who are at standard risk (i.e., do not have risk factors for severe illness).[46]

On October 1, 2021, the therapeutic good administration granted provisional determination to Pfizer Australia in relation to a new combination medicine containing PF-07321332 and ritonavir, for the treatment of adult patients with symptomatic, confirmed coronavirus infection. Pfizer is also evaluating an intravenously administered investigational protease inhibitor, PF-07304814. This candidate is being analyzed in a Phase 1b multi-dose trial in hospitalized COVID-19 patients.

Molnupiravir (Moln)

The drug was developed at Emory University by Drug Innovation Ventures. Ridgeback biotherapeutics partnered with Merck and Co. to develop the drug further, thus Moln was discovered for the treatment of SARS-CoV-2 infection. It is a prodrug of the synthetic nucleoside derivative N4-hydroxycytidine and exerts its antiviral action through introduction of copying errors during viral RNA replication. It thus inhibits replication of SARS-CoV-2, by lethal mutagenesis.[47]

As the drug can be administered orally, the treatment can be started early and inhibits progress of disease to severe stage. Thus, it shortens the infectious phase to ease the patient isolation and chance of spread. An interim analysis of the Phase 3 MOVe-OUT trial of Moln in non-hospitalized adult patients with mild-to-moderate COVID-19 with symptom onset within 5 days was done. All enrolled patients had at least one risk factor associated with poor disease outcome at study entry. It was observed that Moln significantly reduced the risk of hospitalization or death compared to placebo across all subgroups. Efficacy of Moln was not affected by timing of symptom onset or underlying risk factor. In addition, based on the available viral sequencing data of participants (approximately 40%), Moln demonstrated consistent efficacy across Gamma, Delta, and Mu viral variants.[48]

At the recommendation of an independent Data Monitoring Committee and in consultation with the USFDA, recruitment into the study was being stopped early due to its positive results. Merck is planning to submit an application for EUA to the USFDA as soon as possible based on these findings and plans to submit marketing applications to other regulatory bodies worldwide.

Moln is also being evaluated for post-exposure prophylaxis in MOVe-AHEAD, a global, multicenter, randomized, double-blind, and placebo-controlled Phase 3 study, which is evaluating the efficacy and safety of molnupiravir in preventing the spread of COVID-19 within households. Result of study has yet to analyze. Status of various antiviral drugs which are being tried in COVID-19 are discussed below-

As per literature search, there is no evidence to support use of protease inhibitors for the treatment of COVID-19. There is limited evidence to support that RAM and protease inhibitors such as darunavir nelfinavir may have synergistic effect. Nucleotide/nucleoside reverse transcriptase inhibitor (NRTI) has also shown binding affinity to SARS-CoV2 *in vitro*. NRTIs such as tenofovir and emtrictabamine might exhibit a prophylactic role against COVID- 19.

Some of the anthelmintic agents such as nitazoxanide, niclosamide, ivermectin, and an antirheumatic agent hydroxychloroquine have shown some benefit in COVID-19 infection but

none of the guidelines recommend their use for COVID-19 infection. Backer *et al.* designed a new formulation for niclosamide, named UNI91104, which tried as highly concentrated stock solution optimized for inhalation and nasal application. Therefore, topical aerosol application of niclosamide might be useful, as it may produce high local concentrations in oropharynx, upper and lower airways were that the viral burden is the highest.[49]

The researchers at North-west University Feinberg School of Medicine in the US found a coronavirus-specific pocket in the non-structural protein-nsp16, which is important for viral replication. Nsp16 is considered one of the key viral proteins that could be inhibited by drugs to stop the virus shortly after a person gets exposed. Adding a drug which would only target the invader protein may stop the virus early before the disease progresses.[50]

Searching for effective therapies for COVID-19 infection is still a complex process. How these potential COVID-19 treatments will translate to effective therapy in human is difficult to predict. Even after about 2 years of research and evaluating so many repurposed antiviral agents, none of antiviral drugs are recommended by the WHO for the treatment of COVID-19.

CONCLUSION

Even after 2 years of research none of the antiviral drugs have been proven to be effective and none of antiviral drugs are recommended by the WHO for the treatment of COVID-19. 1 Searching for effective therapies for COVID-19 infection is still a complex process.

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