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Review Article

A review on pharmacokinetics, pharmacodynamics and clinical aspects of remdesivir and favipiravir for the treatment of coronavirus disease

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Abstract

The coronavirus disease has spread all over the world. Till now no medicine, vaccine, and any other monoclonal antibodies have been approved for the diagnosis or prevention of COVID-19. In many countries, doctors are considering “repurposing” different approved drugs like interferon- α , lopinavir/ ritonavir, ribavirin, and chloroquine phosphate, etc. to treat COVID-19. Remdesivir (GS-5734) is a prodrug of monophosphoramidate of adenosine analogue. Remdesivir block the viral RNA dependent RNA polymerase (RdRp). Favipiravir (T-705) is also a prodrug and was revealed during evaluating the antiviral activity of chemical agents concerning the influenza virus. This review summarizes the status, mechanisms, preclinical research, and clinical trial progress of remdesivir and favipiravir for the treatment of COVID-19.

Keywords: coronavirus disease, favipiravir, remdesivir, clinical trials, pharmacodynamics

INTRODUCTION

The world has suffered the most pandemic condition nowadays due to coronavirus disease (COVID-19). In 2019, novel coronavirus originated and now it is rapidly spreading from China (Wuhan City of Hubei Province) to the rest of the world. ^{1, 2} Till now 15 December 2020, there have been 73,353,210 confirmed cases of COVID-19, including 1,631,336 deaths. (<https://www.worldometers.info/coronavirus/>) India has reported 9,912,054 confirmed cases of COVID-19 with 143,802 deaths and the numbers are still increasing day by day. (<https://www.worldometers.info/coronavirus/country/india/>)

The general symptoms of coronavirus include cough, fever, shortness of breath, and dyspnoea. In most cases, SARS-CoV2 infections can lead to death due to kidney and pneumonia, acute respiratory syndrome, and even multiple organ failure. ^{3, 4} Till now no medicine, vaccine, and any other monoclonal antibodies have been approved for the diagnosis or prevention of COVID-19. In many countries, doctors are considering “repurposing” different approved drugs to treat COVID-19.

Additionally, remdesivir and favipiravir are two drugs now days are approved for treating COVID-19. Remdesivir (GS-5734) is a prodrug of monophosphoramidate of adenosine analogue. Remdesivir block the viral RNA dependent RNA polymerase (RdRp). ⁵ Favipiravir (T-705) is also a prodrug

and was revealed during evaluating the antiviral activity of chemical agents for influenza virus. ⁶

ORIGIN AND LIFE CYCLE OF SARS-COV-2

The SARS-CoV-2 strain was first found when a sample is isolated from a worker who's suffering from pneumonia in the Wuhan seafood market. ⁷ The founded strains of SARS-CoV-2 have a length of 29.9 kb. SARS-Cov-2 has four important structural proteins, which include (a) Spike (S) glycoprotein, (b) small envelope (E) glycoproteins, (c) membrane (M) glycoproteins, (d) nucleocapsid (N) protein, and some adjunct proteins. ⁸ The S glycoprotein having a molecular weight of 150 kDa and it is found in the outer portion of the virus. It is a transmembrane protein. Due to the host cell's furin-like protease, the S glycoprotein is cleaved into their two subunit namely S1 and S2, where S1 is responsible for the identification of the host virus range and cellular tropism and S2 function to mediate virus fusion in the transmitting the host cells. ⁹⁻¹¹

The N Protein or also called nucleocapsid is the structural component of CoV locating in the ER (endoplasmic reticulum)-Golgi region. The N protein is structurally bound to the nucleic acid material of the virus. The N protein proposed to lead the structural changes increasing the affinity for viral RNA. ^{9, 12, 13} The main structure of SARS-CoV-2 and the life cycle of SARS-CoV-2 is shown in Fig.1 and Fig.2.

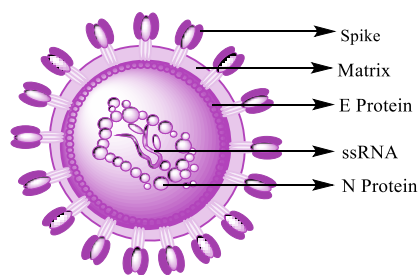


Figure 1: Structure of coronavirus (SARS-CoV-2).

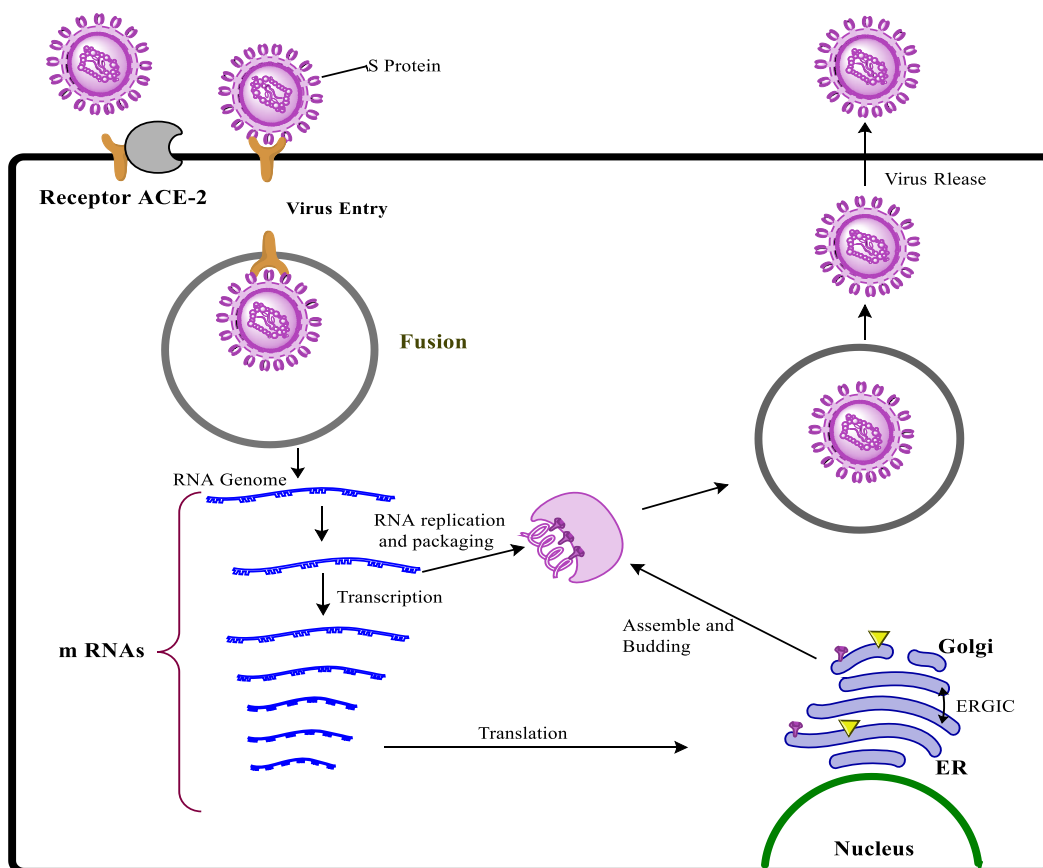


Figure 2: Entry and life cycle of severe acute respiratory syndrome coronavirus. ¹⁴⁻¹⁶

PHARMACOLOGY OF REMDESIVIR AND FAVIPIRAVIR

Remdesivir (GS-5734) is a phosphoramidate prodrug, which inhibits the viral RNA dependent RNA polymerase (RdRp). As RdRp is showing extremely conserved across coronavirus due to its non-structural proteins (nsp12) making it an attractive target for broad-spectrum antiviral drugs. The essential clinical sign of remdesivir is for the treatment of

Ebola virus (EVD) disease but due to the poor efficacy of remdesivir in phase III of clinical trials, it has not been approved for sale for any country. Now remdesivir has been revealed to utilize its activity against the coronavirus Middle East respiratory syndrome-related coronavirus (MERS-CoV) and SARS-CoV). Recently in vitro studies indicated that remdesivir shows an effective action for the treatment and controlling of SARS-CoV-2 infection. ¹⁷⁻²⁰

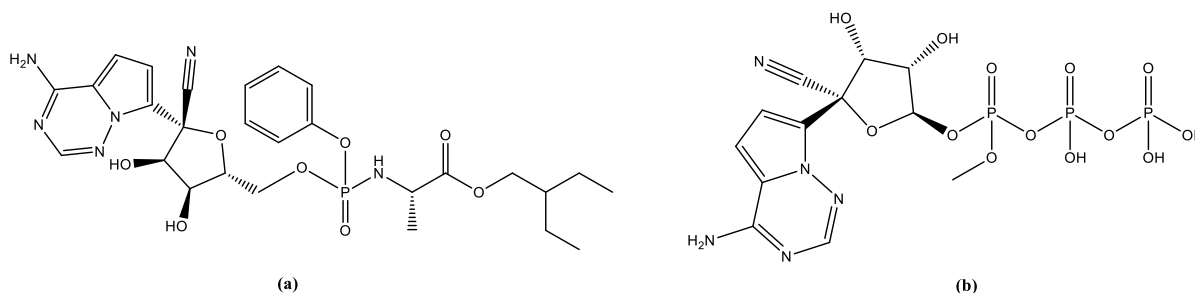


Figure 3: Chemical structures of (a) remdesivir as the phosphoramidate prodrug of an adenosine C-nucleoside and (b) pharmacologically active nucleoside triphosphate (NTP) as a viral RdRp inhibitor.

Favipiravir was the first drug used in Wuhan (China) for the treatment of the SARS-Cov-2 virus (coronavirus-COVID-19), when the virus spread all over the world than various countries received the approval of the favipiravir to use a drug as in emergency basis. ^{21, 22} In June 2020, it received approval from DCGI in India for mild and moderate COVID-

19 infection. Favipiravir (T-705) is an oral antiviral drug firstly used against the influenza virus and lately, it was used for the treatment of Ebola Virus. Favipiravir (T-1105) a lead compound and its derivatives were found to have antiviral activities. Chemical modification of the pyrazine moiety of T-1105 leads to the formation of favipiravir. ^{23, 24}

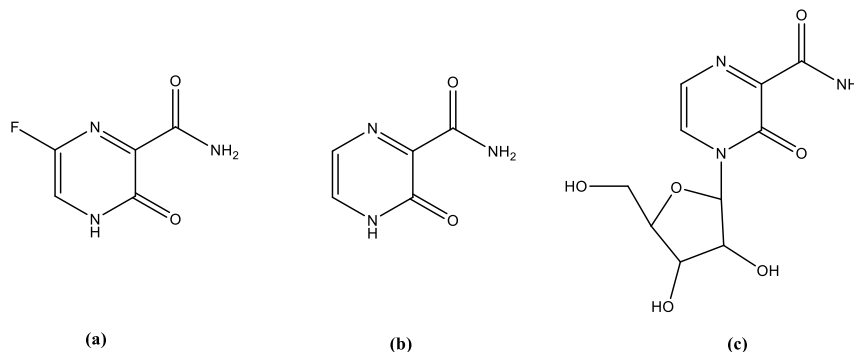


Figure 4: Chemical structures of favipiravir (a) T-705 (b) T-1105 (c) T-1106.

PHARMACOKINETICS AND PHARMACODYNAMICS OF REMDESIVIR AND FAVIPIRAVIR

Remdesivir is a prodrug. Remdesivir is generally administered through IV injection with a dose of 200mg for adults in one day, followed by the maintenance dose of 100mg for adults up to 10days. Plasma half-life ($T_{1/2}$) of remdesivir is 1hr and their metabolites; alanine metabolite GS-704277 shows plasma half-life 1 hr, nucleoside monophosphate metabolite GS-441524 is 24.5hrs. Remdesivir shows moderate protein binding up to 12.1%. However, metabolites of remdesivir GS-704277 and GS-441524 exhibit low plasma protein binding with a mean free fraction of $\geq 85\%$. Most of the drug is eliminated through urine (74%) and the rest of the drug is eliminated through faeces. Remdesivir is a prodrug of a nucleoside analogue, which is used to inhibit the action of RNA polymerase. As it is given once a day, the duration of action is moderate. ²⁵⁻²⁸

Favipiravir is an orally administered prodrug, having shown greater bioavailability $\sim 94\%$. It has a low volume of distribution (10e20L) and having a protein binding of 54%. The maximum concentration of drug reaches to plasma in a single dose with 2hrs. However, in multiple dosing T_{max} and half-life increases. Generally, favipiravir has a short half-life (2.5h) and rapidly eliminated by renal elimination in the hydroxylated form. It exhibits dose-dependent and time-dependent pharmacokinetics. As favipiravir is not metabolized by the cytochrome P450 system but inhibits the CYP2C8 component. Therefore, caution must be needed when co-administered with drugs, which are metabolized by the CYP2C8 systems. ^{6, 29-31}

MECHANISM OF REMDESIVIR AND FAVIPIRAVIR

Remdesivir is a phosphoramidate prodrug of an adenosine C nucleoside. As it is a prodrug, when a drug is entered into the respiratory epithelial cells in the body, this will be metabolized into its active form i.e. nucleoside triphosphate. ³²

The active form of remdesivir can prevent the replication of many coronaviruses in the lung epithelial cells. SARS-CoV-2 is an enclosed, positive-sense, RdRp, which is coded by the virus itself, dominates single-stranded RNA virus. After the virus attacks the host cell, the viral genomic RNA is straight used as a template, and the host cell protein synthesis system is used for the translation of RdRp. ^{33, 34} RdRp is continuously used to complete the transcriptional synthesis of the negative-strand subgenomic RNA, the synthesis of several structural protein-related mRNAs, and the replication of viral genomic RNA. RdRp can precisely and efficiently synthesize tens of thousands of nucleotides and thus enables all other biological actions after the virus attacks the host cell. Most of the anticoronavirus drugs targeting RdRp are nucleoside analogues. This decreases viral RNA synthesis. ^{28, 35, 36}

Studies are continuing to understand whether the prodrug terminates RNA chains or it causes mutations in the RNA. Using Ebola virus studies, it was well known that the prodrug, Remdesivir, inhibited the action of RNA-dependent RNA polymerase, producing the elongation of the synthesized chain. The mechanism of action of remdesivir is shown in Fig. 5. ³⁷

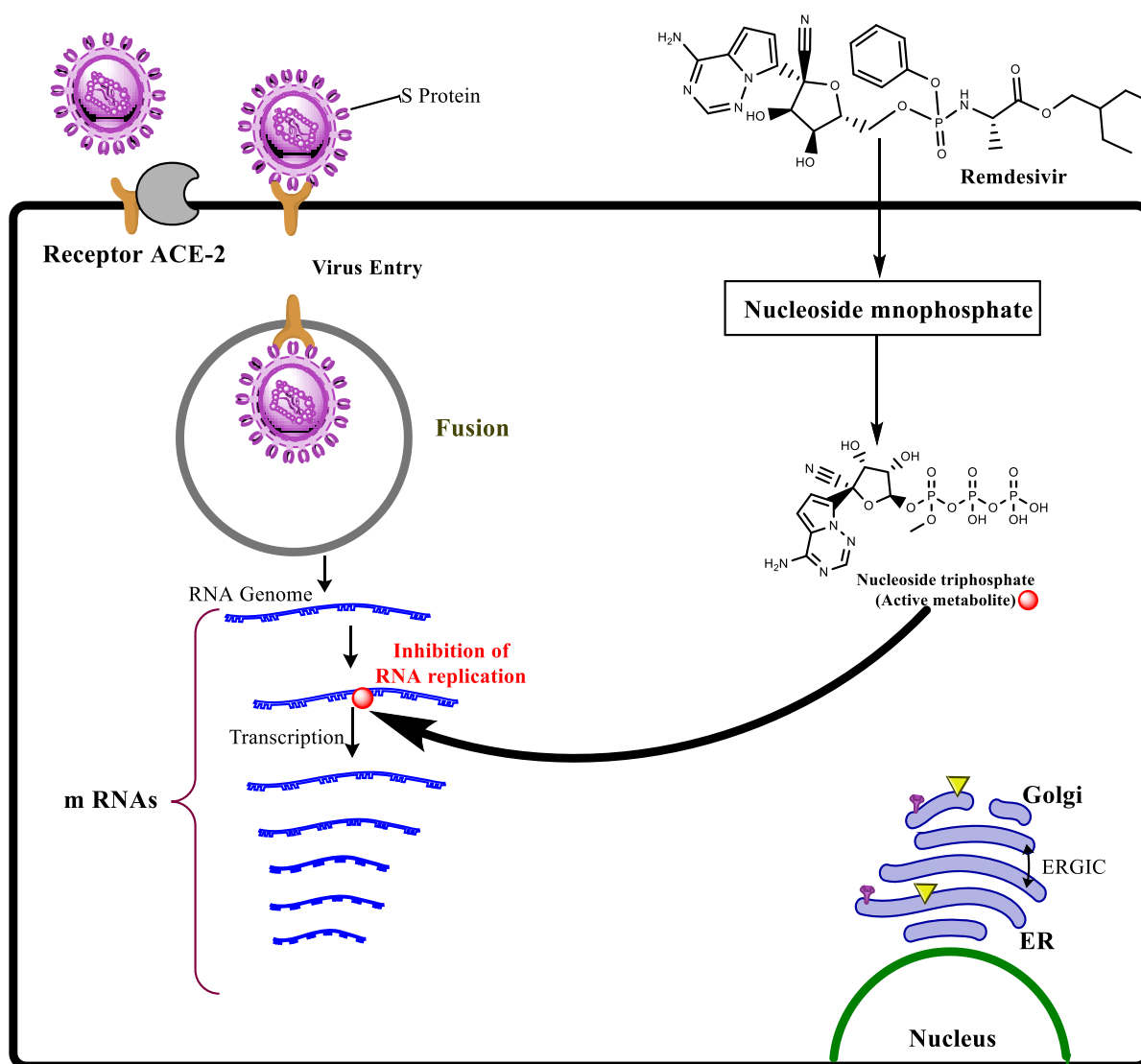


Figure 5: Mechanisms of action of remdesivir.

Favipiravir undergoes phosphor-ribosylation to its active form favipiravir-RTP within the tissue. It shows the antiviral effect through a different mechanism:

(a) The activities for the favipiravir i.e. favipiravir-RTP acts as a substrate for the RNA-dependent RNA-polymerase (RdRp) enzyme. Thus inhibiting its action primary to the elimination of viral protein synthesis. ⁶

(b) The active form preventing the extension of an RNA strand by combined preventing with the viral RNA strand.

(c) Recently it has been revealed that favipiravir shows lethal mutagenesis in-vitro during influenza virus infection that makes favipiravir a virucidal drug. Whether the same action is revealed against SARS-CoV-2 or not is undefined (Fig. 6). ^{23, 24, 38, 39}

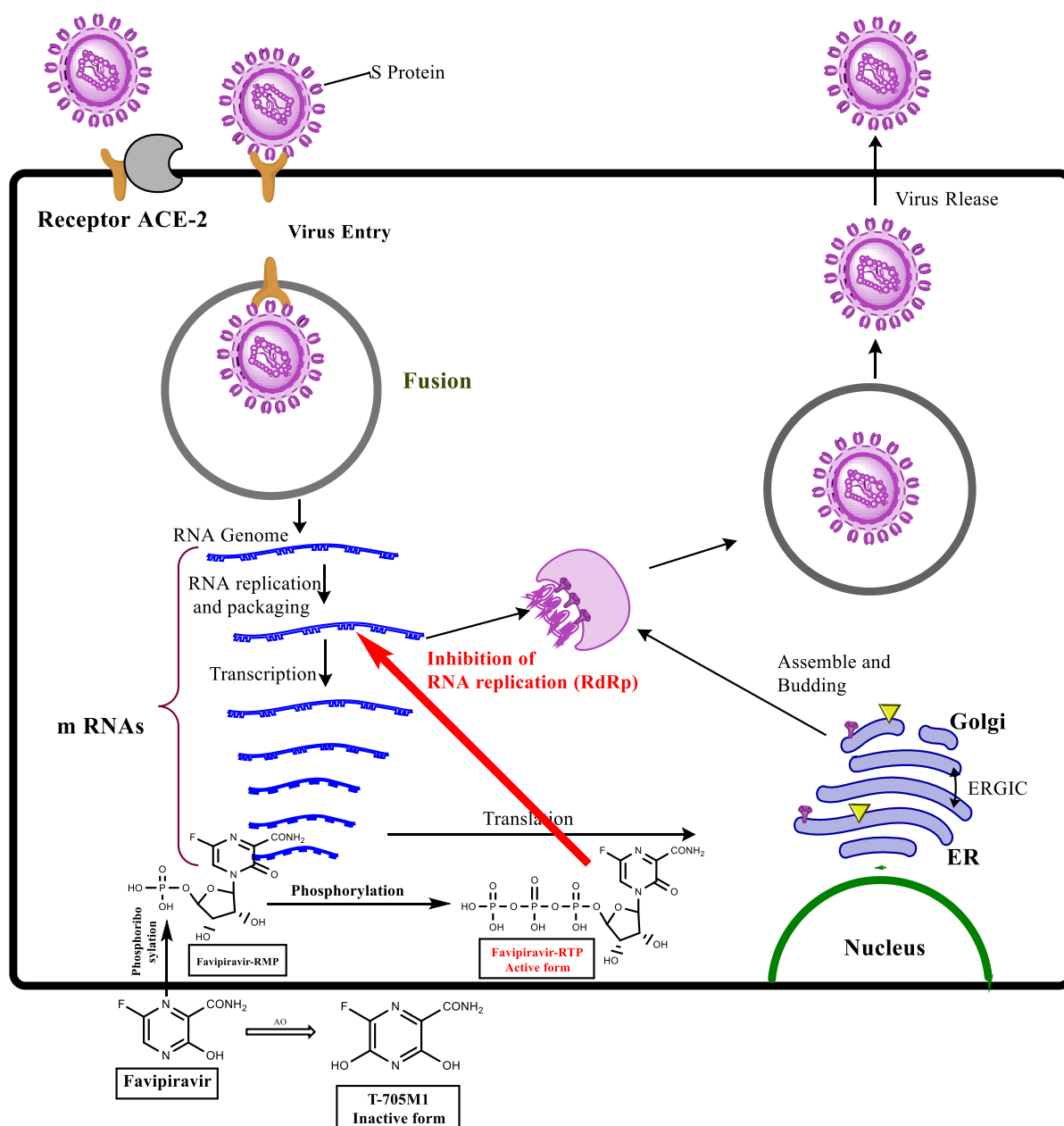


Figure 6: Mechanism of action of favipiravir (T-705) against the virus. Favipiravir is incorporated into cells and converted to favipiravir ibofuranosyl-5'-triphosphate (favipiravir-RTP) by host cells. The triphosphate form, favipiravir-RTP, inhibits the activity of RNA-dependent RNA polymerase (RdRp) of RNA viruses. AO, aldehyde oxidase; RMP, ribosyl monophosphate. ⁴⁰

CLINICAL ASPECTS OF FAVIPIRAVIR

Favipiravir (T-705 or Avigan), an oral antiviral medication recognized in Japan for flu contamination in 2014. It has likewise been utilized for the treatment of Ebola infection disease. It acts by direct restraint of viral replication and records through misincorporation in nascent vRNA (viral ribonucleic corrosive), or by binding to preserved polymerase domains, preventing incorporation of nucleotides for vRNA replication and transcription. ^{6, 41}

According to Madelain V et al ⁴² nonhuman primate (NHP) model investigation, favipiravir was found to have a versatile safe response in viral clearance and can turn into a treatment choice for other arising viral infections. Different investigations have additionally revealed that favipiravir demonstrations by Inhibiting RNA dependent RNA polymerase (RdRp) by changing over into its dynamic metabolite (favipiravir-ribofuranosyl-50-triphosphate (RTP)) in cells and is perceived as a substrate by viral RNA polymerase. As SARS-CoV-2, is an RNA infection, this

medication may be one of the choices for treating COVID-19. ^{43, 44}

National Medical Products Administration of China has included this medication for the expected therapies for COVID-19. The clinical evidence on the feasibility of this medication was seen in the clinical trials conducted by the Third People's Hospital of Shenzhen in Guangdong region, where favipiravir group patients' (n ¼ 35) lab tests indicated negative for COVID 19 following 4 days of therapy, while other group patients took 11 days for the same.

In an open-label non-randomized control study led by Q Cai et al, favipiravir (FPV) 1600 mg twice day by day as a loading dose and 600mg twice every day in addition to interferon (IFN). In another group lopinavir 400 mg/ritonavir 100mg (RTV) twice every day in addition to IFN. They noticed a limited viral clearance time and significant improvement in chest imaging in the FPV group with few ADRs. ⁴⁵

At present, there are 17 clinical trials specific to COVID-19 that are at different periods of improvement and analysts are

expecting promising outcomes in clearing the virus.³⁵ Recently, a reputed organization has started Phase-3 clinical trials for COVID-19 in India with tablet favipiravir, and it is expecting the overall investigation results by August (<https://www.thehindu.com/news/national/glenmark-begins-phase-3-clinical-trials-on-antiviral-drug-favipiravir-for-covid-19-patients-in-india/article31563198.ece>).

Recently, a stage 3, open name, randomized, multicenter study (CTRI/2020/05/025114, Glenmark Pharmaceuticals) was started in India to decide the adequacy of favipiravir in patients infected with mild to moderate COVID-19 under the worldwide trials progressing for this medication (http://www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=43504&EncHid=&modid=&compid=%27%2743504det%27/2020). Registered clinical trials of favipiravir are shown in Table 1.

The investigation enlisted patients with both mild (N = 90) and moderate (N = 60) COVID-19 by separated randomization based on baseline disease severity. The essential target of this investigation was to assess the clinical acceptability and safety of favipiravir combined with standard supportive care. The essential endpoint was time until the end of oral shedding of SARS-CoV-2 infection. The secondary endpoints included — the time from randomization to clinical cure based on clinician assessment, rate of clinical cure at day 4/7/10/14, rate of SARS-CoV-2 RT-PCR negativity at day 4/7/10/14, and time from randomization to hospital discharge. The total length of study support had been a limit of 28 days from the day of randomization. The outcomes from this examination will be significant in the further validation of global evidence on the adequacy and safety treatment against COVID-19.

CLINICAL ASPECTS OF REMDESIVIR

With the COVID-19 outbreak growing in size and an absence of alternative therapeutics, two clinical trials applying remdesivir were planned and started in China.

On February 5, 2020, a phase 3 randomized, quadruple-blind, placebo-controlled clinical trial was registered at Capital Medical University, to determine the safety and efficacy of remdesivir in patients with mild to moderate SARS-CoV-2 infection (NCT04252664, since suspended).

A day later, a subsequent trial (NCT04257656 since terminated) was enrolled at a similar area focused on patients with progressive COVID-19 respiratory disease. Both trials had planned to trail the primary outcome as a time to clinical enhancement, up to 28 days. Both trials provided remdesivir as a 200 mg loading dose on the first day, with 9 succeeding days of maintenance dosing at 100 mg; this regime is equal to that utilized in the previous NCT03719586 Ebola trial, which performs to be the model

for all succeeding trials involving remdesivir (discussed below; Table 2, registered trials of remdesivir).⁴⁶⁻⁴⁸

Goldman et al (2020) did randomized, open-label, phase 3 trials including hospitalized patients with COVID-19. Patients were randomly partitioned to get 5-day and 10-day courses of the intravenous remdesivir. In patients with extreme Covid-19 not requiring mechanical ventilation, there was not any difference between the 5-day and 10-day periods of the intravenous remdesivir. Due to the lack of placebo control, the degree of benefit cannot be determined (ClinicalTrials.gov number: NCT04292899).²⁷

Wang et al (2020) led a randomized, double-blind, placebo-control multicenter trials in adult patients with COVID-19 at ten hospitals in China (ClinicalTrials.gov number: NCT04257656). The 237 patients were randomly separated into the remdesivir (158 cases) and placebo groups (79 cases). Results showed that remdesivir administration is not recognized with a significant change in the time of clinical improvement. However, patients who received remdesivir had a numerically shorter recovery time compared to those who received placebo.⁴⁹

A few clinical trials of intravenous remdesivir to treat COVID-19 are ongoing. A double-blinded, placebo-controlled trial (ClinicalTrials.gov identifier: NCT04280705) is in progress in the USA in which patients are randomly isolated into two placebo and remdesivir groups. In the remdesivir groups, patients get 200 mg of parenteral remdesivir as an initial dose on the first day, and a maintenance dose of the drug (100 mg once daily) while hospitalized for up to 10 days. The primary outcome of the trial is time to recovery.

A randomized, phase 3 clinical trial of 5 versus 10 days of remdesivir, sponsored by Gilead Sciences, is selecting patients with severe COVID-19 (ClinicalTrials.gov identifier: NCT04292899). Another phase 3, randomized trial of remdesivir (ClinicalTrials.gov identifier: NCT04292730) is the same as NCT04292899 except patients enrolling in that study suffer moderate COVID-19. The main outcome is the number of patients discharged by day 11.

To access the efficacy and safety of intravenous remdesivir China employing two double-blinded, placebo-controlled trials. 308 targets with mild to moderate COVID-19 hospitalized adults for one trial (ClinicalTrials.gov identifier: NCT04252664) and second trials (ClinicalTrials.gov identifier: NCT04257656) targets 452 hospitalized adults with severe COVID-19. In both trials, the initial dose of remdesivir is 200 mg on day 1, followed by 100 mg once daily for the remaining days. In both trials, the main outcome measure is the time to clinical recovery.³³

To investigate the safety and efficacy of remdesivir for COVID-19, currently, ten clinical trials are registered (Table 2).

Table 1: Registered clinical trials of favipiravir for the treatment of COVID-19. ⁴⁰

Registration number	Design	Intervention	Outcomes
ChiCTR2000029544	Randomized controlled trial	Group A (n = 10): Antiviral treatment + BaloxavirMarboxil tablets. Group B (n = 10): Antiviral treatment + favipiravir tablets. Group C (n = 10): Antiviral treatment.	Time to viral negativity by RT-PCR. Time to clinical improvement.
ChiCTR2000029548	Randomized, open-label, controlled trial	Group A (n = 10): BaloxavirMarboxil: 80 mg on day 1, 80 mg on day 4; 80 mg on day 7 as necessary. Group B (n = 10): Favipiravir: 600 mg t.i.d. with 1,600 mg first loading dosage, no more than 14 days. Group C (n = 10): Lopinavir-Ritonavir: 200 mg/50 mg, twice daily, for 14 days	Time to viral negativity by RT-PCR. Time to clinical improvement: Time from start of study drug to hospital discharge or to NEWS < 2 for 24 hours.
ChiCTR2000029600	Randomized controlled trial	Group A (n = 30): Alpha-interferon atomization. Group B (n = 30): Lopinavir and Ritonavir + alpha-interferon atomization. Group C (n = 30): Favipiravir + alpha-interferon atomization.	Declining speed of SARS-CoV-2 by PCR. Negative time of SARS-CoV-2 by PCR. Incidence rate of chest imaging. Incidence rate of liver enzymes. Incidence rate of kidney damage.
ChiCTR2000029996	Randomized controlled trial	Group A (n = 20): Favipiravir tablets; 200 mg; oral; twice a day. The adult dose is 1,600 mg per time on first day; treatment: 10 days. Group B (n = 20): Favipiravir tablets; 200 mg; oral; twice a day. The adult dose is 1,800 mg per time on the first day; treatment: 10 days. Group C (n = 20): Favipiravir tablets; 200 mg; oral; twice a day. The adult dose is 2,400 mg per time on first day; treatment: 10 days.	Time to clinical recovery.
ChiCTR2000030113	Randomized controlled trial	Group A (n = 15): Keep ritonavir/ritonavir treatment. Group B (n = 15): Favipiravir	Blood routine tests. Liver function examination. Renal function examination. Blood gas analysis. Chest CT examination.
ChiCTR2000030254	Randomized controlled trial	Group A (n = 120): Favipiravir tablets. Group B (n = 120): Arbidol tablets.	Clinical recovery rate of day 7.
ChiCTR2000030894	Randomized controlled trial	Group A (n = 90): Favipiravir combined with Tocilizumab. Group B (n = 30): Favipiravir. Group C (n = 30) Tocilizumab.	Clinical cure rate.
ChiCTR2000030987	Randomized controlled trial	Group A (n = 50): The oral trial drug favipiravir tablets plus chloroquine phosphate tablets. Group B (n = 50): Oral trial drug favipiravir tablets. Group C (n = 50): Oral placebo treatment	Improvement or recovery of respiratory symptoms Viral nucleic acid shedding.
JPRN-jRCTs031190226	Randomized, controlled trial	A prospective multi-centre open trial to assess the safety and efficacy of Favipiravir in patients infected with covid-19.	
PRN-jRCTs041190120	Randomized, open-label, controlled trial	Multicentre, open-label randomised trial of favipiravir in asymptomatic and minimally symptomatic patients infected with SARS-Cov2 to evaluate viral load reduction.	
NCT04273763	Randomized, controlled trial	Evaluating the Efficacy and Safety of Bromhexine Hydrochloride Tablets Combined With Standard Treatment/ Standard Treatment in Patients With Suspected and Mild Novel Coronavirus Pneumonia (COVID-19).	
NCT04310228	Randomized, controlled trial	Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019.	

CT, computed tomography; NEWS, national early warning score; PCR, polymerase chain reaction; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2: Registered Clinical Trials of Remdesivir for the treatment of COVID-19. ³³

Registration Number	Official Title	Status	Country	Estimated Study Completion Date
NCT04257656	A phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of remdesivir in hospitalized adult patients with severe COVID-19	Terminated	China	April 10, 2020
NCT04365725	A multicenter, retrospective study of the effects of remdesivir in the treatment of severe COVID-19 infections	Recruiting	France	June 2020
NCT04302766	An intermediate-size patient population expanded access treatment protocol for coronavirus disease 2019 (COVID-19) using remdesivir (RDV; GS-5734™)	Available	-	-
NCT04252664	A phase 3, randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of remdesivir in hospitalized adult patients with mild and moderate COVID-19	Suspended	China	April 27, 2020
NCT04323761	Expanded access treatment protocol: remdesivir (RDV; GS-5734) for the treatment of SARS-CoV-2 (CoV) infection	Available	-	-
NCT04410354	A phase 2, randomized, double-blind, placebo-controlled study of the efficacy and safety of oral merimepodib in combination with intravenous remdesivir in adult patients with advanced coronavirus disease 2019 (COVID-19)	Recruiting	USA	August 2020
NCT04292730	A phase 3, randomized study to evaluate the safety and antiviral activity of remdesivir (GS-5734™) in participants with severe COVID-19	Active, not recruiting	-	June 2020
NCT04409262	A phase 3, randomized, double-blind, multicenter study to evaluate the efficacy and safety of remdesivir plus tocilizumab compared with remdesivir plus placebo in hospitalized patients with severe COVID-19 pneumonia	Recruiting	-	July 31, 2020
NCT04431453	A phase 2/3, single-arm, open-label study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of remdesivir (GS-5734™) in participants from birth to <18 years of age with COVID-19	Not yet recruiting	-	December 2020
NCT04330690	A multicenter, adaptive, randomized, open-label, controlled clinical trial of the safety and efficacy of investigational therapeutics for COVID-19 in hospitalized patients (CATCO: Canadian Treatments for COVID-19), in conjunction with the Public Health Emergency SOLIDARITY Trial (World Health Organization)	Recruiting	Canada	May 18, 2022

CONCLUSION

Coronavirus disease is spreading across the world day by day, and still there is no vaccine or any other medicine approved for the treatment of COVID-19. Recently, many researchers recommended the use of favipiravir and remdesivir for the treatment of COVID-19. The review concludes pharmacokinetics, pharmacodynamics and clinical trials related with these drugs for combating against the COVID-19. No drug may be superior or inferior, however, the use of single drug may not be effective enough to control this deadly virus, so use of combination of antivirals with different mechanism of action may be more effective and at the same time, their adverse events should not be underestimated.

CONFLICT OF INTEREST: Declared none.

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