



# ACCEPTABLE MEDICATION IN THE TREATMENT OF SEVERE ACUTE RESPIRATORY SYNDROME (SARS) COVID- 19 INFECTION

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## **ABSTRACT-**

In the present scenario of COVID-19, these promising drugs i.e. remdesivir, dexamethasone and favipiravir are a potential treatment option. The deadly SARS-COV-2 virus caused inflammation to the lungs and in severe cases, it leads to multiple organ failure. WHO approved emergency use of both the drugs for the patient who are hospitalized and require oxygen support. On one side, antiviral properties of remdesivir are used against SARS-COV-2, and on the other side, anti-inflammatory responses of dexamethasone are being utilized to treat the lung infection caused by the viral attack. Like any other drug, remdesivir, and dexamethasone, both have side effects. But, in the hour of need, these two have been reported to decrease the mortality rate. So short-term use of these drugs in critical patients is highly fruitful. Favipiravir is another repurposed antiviral agent that has recently come into the limelight for its ability to clear the viremia very rapidly in the early part of the illness.

Keywords: COVID-19, Antiviral, Favipiravir, Remdesivir, Dexamethasone.

## **INTRODUCTION-**

Several respiratory diseases have been reported to date which is affecting the humans such as asthma, emphysema, tuberculosis, etc. there are various causative agents of respiratory diseases which includes varieties of bacteria, virus, fungi, etc. A new outbreak of COVID-19 is causing a serious public health crisis from the year 2019. About 170 million cases with the death toll of 3.5 million. Currently various other conditions like black, yellow, and white fungus, post-COVID symptoms are being observed. Various organizations across the globe are conducting studies to find a proper management tactic for this deadly disease. WHO, Oxford

University, US NIAID, ICMR, etc. are conducting clinical trials for various effective medications.

WHO approved two potential drugs for the treatment of COVID which are remdesivir and systemic corticosteroids (dexamethasone) for the severe cases of COVID patients who are hospitalized and need oxygen support. The studies show a potential effectivity of these two drugs, although there are claims that no or fewer effects are observed on the mortality rate of patients. But still, these drugs stand first in the queue for COVID treatment. Remdesivir being an antiviral drug acts on the viral SARS-COV-2 bodies while dexamethasone has anti-inflammatory properties and thus helpful in the treatment of pneumonia-like symptoms of this disease. Here we are discussing aspects related to both the medications along with favipiravir that has been approved by DCGI for clinical trials. Favipiravir is a medication that has been used in Japan since 2014, primarily against the influenza virus. It has also shown activity against covid-19 in some settings. The mechanism of action of favipiravir is similar to the remdesivir as both are selective inhibitors of viral RNA polymerase. The two positives of favipiravir over remdesivir are that it is available orally and it is not expensive.

## REMDESIVIR

Remdesivir is an antiviral agent that was developed by the company Gilead Sciences (US) under the name GS-5734. It is started with the treatment of viral hepatitis, as well as a cold-like virus called respiratory syncytial virus (RSV). Because of its initial response against the COVID-19, the US FDA approved this drug to treat COVID-19. In India, the Department of Health also recommended that it is an investigative treatment in their draft COVID-19 protocol document, however, he clarified that it isn't a "life-saving drug" but because, we will use Remdesivir as we don't have an antimicrobial drug. Remdesivir has been proven to be useful for those in hospitals and on oxygen...it cannot be considered a standard antibiotic.

This anti-viral drug should only be given to those people who have been hospitalized and who fall for oxygen supplementation, and who have had chest X-rays or CT scan. There has been much debate and discussion about the effectiveness of Remdesivir in COVID-19 patients. While some studies suggest that the drug does not affect the deadly virus, others say that it shortens the recovery time of patients with COVID. According to a trial by Solidarity by the World Health Organisation which monitors the effectiveness of Remdesivir against COVID-19, it has been found that Remdesivir dose does not do as well as hospital mortality control, but has not been able to prevent COVID -19 related deaths.

It is said to be effective in the complex and critical phases of COVID-19. However, it was also understood to be 'hepatotoxic', (damaging liver cells). According to a WHO study, Remdesivir failed to prevent patient mortality but could reduce hospital stay by 1-3 days. According to experts, the drug should be given to patients who have no symptoms, who have a minor illness, or who are chronically ill and who suffer from multiple sclerosis.

However, it can be used between the second and tenth day of infection to improve its effectiveness among patients with a moderate or moderate infection that progress directly. The doctor prescribes a good course of six doses over five days (on the first day 200mg followed by 100mg for the subsequent 4 days), and will not be overused. Remdesivir is an intravenous nucleotide prodrug of an adenosine analog first developed during the 2013 Ebola epidemic. An analog of the nucleoside novel with a wide range of antibodies between RNA viruses, including ebolavirus (EBOV) and the Middle East respiratory coronavirus (MERS-CoV),

SARS-CoV, and SARS-CoV-2. Originally described in 2016, the drug was taken from a library of small molecules aimed at targeting RNA viruses.

In vivo, re-exposure showed therapeutic and prophylactic effects on a variety of EBOV animals, MERS-CoV, SARS-CoV, and SARS-CoV-2 infections. However, the item failed in clinical trials with ebolavirus disease (EVD), where it was under antibodies investigated in the short-term analysis. Since there was no placebo control in this study, no conclusions about its efficacy in EVD can be made. On the other hand, data from a placebo-controlled trial show beneficial effects for patients with COVID-19. Remdesivir reduces the recovery time of patients in hospitals who need more oxygen and can have a positive effect on death outcomes while having a good safety profile.

What clinical trials and guidelines mean the usage of remdesivir:

ACTT-1 has shown a reduction in time in clinical development and, in a small group analysis, the benefit of dying in patients who need more oxygen but not less oxygen. However, SOLIDARITY did not show any benefit in dying from the use of remdesivir. Trials had different basic concepts and thus they differed in structure and were given the power to test themselves. The main end of ACTT-1 was a time to improve clinics- they were not empowered to die. SOLIDARITY is endowed with the ability to die but was not designed to test groups in time for clinical development or in terms of non-ventilated air compared to air-less air. IDSA guidelines indicate that remdesivir is used in those patients in hospitals with severe COVID-19 (defined as patients with  $SpO_2 \leq 94\%$  in the room, or patients in need of additional oxygen, mechanical ventilation, or extracorporeal mechanical oxygenation) with those patients with potent COVID-19 in extra oxygen but not in ventilation or ECMO, IDSA recommends treatment with five days of rehabilitation instead of 10 days of rehabilitation and those COVID-19 patients without the need to add oxygen and with oxygen saturation  $>94\%$  in room temperature, IDSA recommends against the common use of remdesivir.

The World Health Organization guidelines suggest that it can be rehabilitated without clinical trials for COVID-19 for any serious illness.

National Institutes of Health guidelines recommend the use of rehabilitation of COVID-19 patients in hospitals in need of extra oxygen through the nasal cannula. For patients requiring oxygen with a high flow device or inactive ventilation, remdesivir and dexamethasone can also be used in hospital patients who need ventilation or newly fitted ECMO, remdesivir and dexamethasone can be considered.

Virus prevention through a regeneration: As in fig.1 internal administration of remdesivir (GS-5734) and prevention of coronavirus recurrence. Passing the cell edge with remdesivir is aided by the part of the prodrug attached to the nucleoside content. Upon entering the target cell, the pro-nucleotide continues with other phosphorylation steps to become an active triphosphate metabolite that effectively inhibits the replication of viral RNA. Delayed chain depletion is caused by the following processes:

- (i) Separation of nucleoside triphosphate (NTP) in RNA duplication RdRp.
- (ii) Preventing further chain expansion after NTP and 3 nucleosides.
- (iii) Premature termination of RNA synthesis.

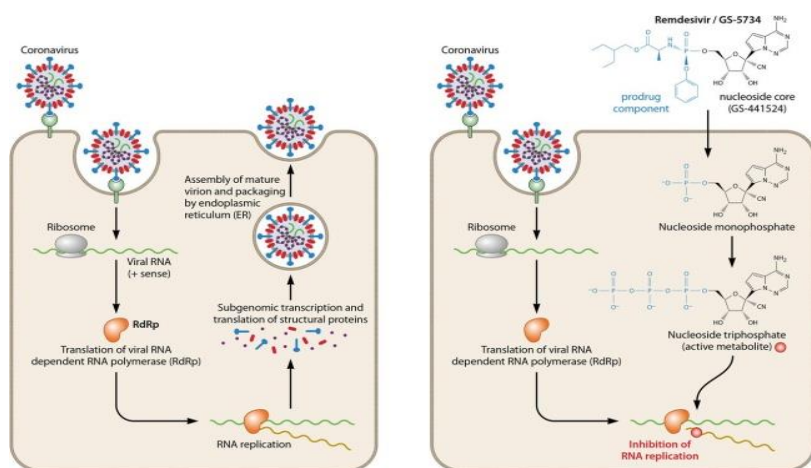


Fig.1 Process of inhibition of virus

## DEXAMETHASONE-

Dexamethasone is a very potent and highly selective glucocorticoid drug. It is found to be 30 times more active than cortisone. Dexamethasone also has immunosuppressor activity. It is a synthetic long-acting ( $t_{1/2} > 36$  hrs) adrenocorticosteroid with minimal mineralocorticoid activity. It is mainly used as an anti-inflammatory agent but has application in several other conditions like lung infection, skin infection, cancer treatment, allergy treatment, and treatment of tuberculosis, etc. Irrespective of the type of injury, the inflammatory responses are suppressed by dexamethasone. It was approved by FDA in 1958 to use as an anti-inflammatory agent. In recent times, the drug is being used in the treatment of COVID-19. WHO recommended corticosteroids (dexamethasone and hydrocortisone) for severe and critically ill COVID-19 patients, who were in requirement of ventilator support under medical supervision.

WHO also strongly quotes that steroid treatment should not be given to the patients with mild and non-severe patients of COVID-19. Dexamethasone is administered 0.5-5 mg/day through oral and intravenous routes for the treatment of inflammation. Review of 8 randomized studies involving more than 7000 patients under the vigilance of WHO found that the systemic administration of dexamethasone decreased mortality in the study group.

The recent Coronavirus which is a severe acute respiratory syndrome (SARS)-CoV-2 is associated with multiorgan disease, has high morbidity and mortality cases due to autoimmune destruction of the lung by the effect of pro-inflammatory cytokines, chemokines, adhesion molecules, inflammatory enzymes, and receptors. All these effects lead to severe asthma or acute respiratory distress syndrome (ARDS). The SARS-CoV-2 particles activate the epithelial cells of the lungs to produce and release multiple inflammatory proteins, such as chemokines, cytokines, lipid mediators, and growth factors. Dexamethasone is a glucocorticoid and hence it prevents the inflammation-causing substance like cytokines which further reduces lung infections and ultimately improves the patients' condition. On the molecular level, dexamethasone also activates anti-inflammatory genes like annexin-1 (lipocortin-1), SLPI, interleukin-10 (IL-10), and  $I\kappa B-\alpha$ , and ultimately reduces the number of inflammatory cells like eosinophils, mast cells, T-lymphocytes, etc (fig.2).

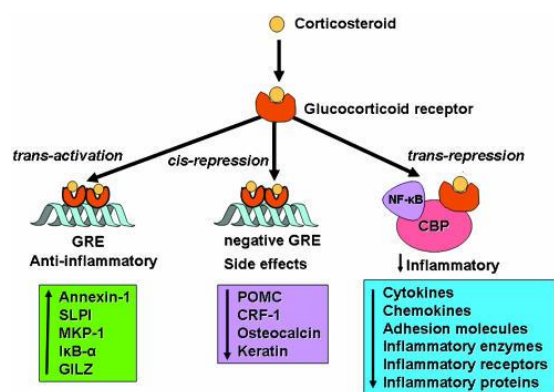


Fig.2. Mechanism of action of corticosteroid(dexamethasone)

Defense against the COVID-19 virus requires activated T cells and specific antibodies. Cytokines are responsible for the severe effects of COVID-19 that damage the lungs. Dexamethasone would limit the production and damaging effect of the cytokines and also inhibit the protective function of T cells, and block B cells from making antibodies, potentially leading to decreased antibodies and reduced immunity caused by the T cells and B cells. Dexamethasone also blocks macrophages from clearing secondary, nosocomial infections. Hence, dexamethasone may be useful for the short-term in severe, intubated, COVID-19 patients, but could be dangerous during recovery since the virus will not only persist but the body will be prevented from generating protective antibodies. But amidst all these aspects the use of dexamethasone is beneficial as the drug successfully shown to reduce the cytokines and other inflammatory mediators caused by SARS-CoV-2 with evidence of the shorter duration of supplemental oxygen therapy for the critically ill patients as well as a reduction in mortality by one-third in patients requiring mechanical ventilation.

Potential side effects of dexamethasone include hyperglycemia. Prolonged use may cause adverse effects like glaucoma, cataract, hypertension, weight gain, and psychological effects. Due to potential changes in hyperglycemia, the use of dexamethasone for a diabetic patient is a matter of concern. The use of prednisolone and hydrocortisone is recommended for pregnant women instead of dexamethasone.

## FAVIPIRAVIR

Favipiravir also known as (T-705), a purine nucleic acid analog, acts as a mutagen with different options for altering viral RNA mutations by incorporating good and invasive RNAs that cause fatal viral mutagenesis which may be difficult to differentiate influenza viruses resistant to favipiravir in labs or mutate clinical resistance. Favipiravir was approved in Japan in 2014 as a treatment for recurrent flu infections. Favipiravir is also considered a comprehensive antiviral with a functional spectrum marked against a variety of RNA viruses and a good oral antiviral drug with > 97% bioavailability.

It has already shown its safety as it has received a FDA indication for a drug-resistant Flu. There has been growing evidence of positive effects against COVID-19 in relation to HIV and the immediate noticeable relief of moderate COVID-19 patients. Due to its antibacterial properties, it inhibits RNA-dependent RNA polymerase (RdRp) viral RNA. Favipiravir was obtained by examining the chemical library of anti-viral activity by the flu virus by Toyama Chemical Co., Ltd. Favipiravir is subjected to intravenous phosphorylation to form an active

form, favipiravir-RTP (favipiravir ribofuranosyl-5'-triphosphate), known as the RdRp substrate, and inhibits the activity of RNA polymerase. Since the RdRp domain is maintained between different types of RNA viruses, this mechanism supports many anti-favipiravir activities.

Favipiravir is effective in a variety of viral strains, including viruses that are resistant to existing antiretroviral drugs. Significantly, favipiravir exhibits antibacterial activity compared to other RNA viruses. Favipiravir is induced into viral RNA by defective RdRp, leading to chain breakdown and viral mutagenesis. The RdRp present in various types of RNA viruses activates many of the anti-viral activities of favipiravir after the introduction of the RNA virus, favipiravir-RTP acts as a mutagen, capable of escaping coronavirus repair machines. Favipiravir-RTP adds pressure to the content of CoV nucleotide, which already has a low cytosine (~17.6%) in the SARS-CoV-2 gene. Overall, along with the frequency of genetic mutations, favipiravir-RTP has a positive effect on SARS-CoV-2 with a cytopathic effect, caused by a virus, reducing the amount of RNA virus, and infectious particles. Favipiravir has a strong bond that binds to RdRp with arrival values of .96.925. Therefore, favipiravir targets the Achilles heel (RdRp complex) of SARS-CoV-2. This unique anti-viral agent will make favipiravir a promising drug for untreated RNA virus infection. It can therefore be used in the treatment of COVID -19 virus but not in death. In India, Glenmark Pharmaceuticals has obtained approval from the Indian drug regulator for the antiretroviral drug favipiravir for the treatment of COVID-19 middle- and middle-aged patients.

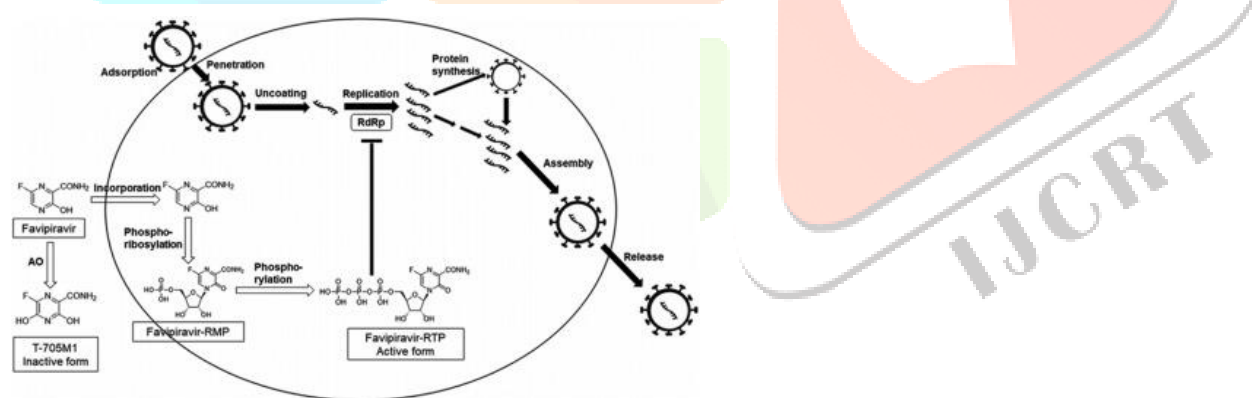


Fig.3. Mode of action of favipiravir in SARS-CoV-2 virus

But its local approval was severely restricted as its use of clinics required government approval, which only allowed potentially dangerous diseases and the same cautious attitude was also adopted in China. In addition, a complex pharmacokinetic profile and a lack of interaction between favipiravir drugs and antiretrovirals have confirmed that current clinical trials do not use a well-designed dose or duration of treatment especially in patients with severe disease. Importantly, the Japanese Drug Safety Bureau, perhaps because of limited safety data, recommended that favipiravir be avoided where alternative therapies were used and adverse effects such as hyperuricemia and teratogenicity / embryotoxicity from favipiravir on human and four different types were reported.

## CONCLUSION

Comparatively, the mode of action of both the drugs are different, remdesivir is an antiviral agent while dexamethasone has anti-inflammatory properties. Both the drugs are found to have a promising therapeutic effect against the severe cases of COVID-19. Despite several different study results and clinical trials, these two drugs came up as a boon in the treatment of this deadly disease. As discussed earlier, remdesivir block the RdRp and the RNA chain truncating of the SARS-CoV-2, and also work against the viral nonstructural protein (nsp14) which has a significant role in viral replication together with the proofreading activity to avoid any mutagenesis while the dexamethasone has been found to reduce the activity and number of the inflammatory particles in the epithelium of lungs like cytokines, chemokines, lymphocytes, etc. and thus showing anti-inflammatory responses.

Dexamethasone also activates anti-inflammatory genes like annexin-1 (lipocortin-1), SLPI, interleukin-10 (IL-10), and  $\text{I}\kappa\text{B-}\alpha$ . It has the potential to reduce the mortality rate in COVID cases and thus dexamethasone is considered as a “breakthrough” treatment of the severe COVID-19 patients. Although both the drugs have their adverse effects but are an effective choice of immediate treatment for COVID-19. Since there has been no large randomized controlled trial, we can not claim that favipiravir is effective. Though there is another school of thought which suggests that favipiravir may be given to patients having mild illness to help in clearing out the viral load. In general, favipiravir does not have much role in the treatment of covid-19.

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