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Review Article

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REVIEW: COMPREHENSIVE STUDY OF DRUGS USED IN COVID 19 AND THEIR MODES OF ACTION

Atul Dilip Muthal*, Nilam Subhash Patangare*, Divya Goraksha Thite, Rashmi Ramesh Pawar

M.Pharm, Department of Pharmaceutical Quality Assurance Techniques, MET's Institute of Pharmacy, BKC, Nashik, Maharashtra.

***Corresponding Author: Atul Dilip Muthal**

M.Pharm, Department of Pharmaceutical Quality Assurance Techniques, MET's Institute of Pharmacy, BKC, Nashik, Maharashtra.

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ABSTRACT

The focus of the review is that Hydroxychloroquine is the drug primarily used to treat the covid virus. Acute Respiratory distress syndrome is a severe form of acute respiratory distress corona virus is a new and quickly spreading virus that causes corona virus illness. In 2019, Hydroxychloroquine and Chloroquine were both used against COVID-19. Favipiravir has a large margin of efficacy against various single-stranded RNA viruses, is well tolerated in humans, and has a strong barrier to resistance, depending on its mode of action and safety. Remdesivir is an analog of nucleotide prodrug that mainly inhibits SARS-CoV-2 RdRp. Its viral activities against SARS-CoV-2 have been shown both in *vivo* and *vitro* studies and are the most promisingly used till date due to its antiviral nature.

KEYWORD: Corona virus, Hydroxychloroquine, Favipiravir, Remdesvir, Mechanism.

INTRODUCTION

Corona viruses are a type of enclosed virus that has a positive-sense RNA genome. This is a single-stranded RNA genome that can infect both animal and human species. Those that cause the common cold, severe acute respiratory syndrome corona virus (SARS), Middle East Respiratory syndrome-related coronavirus (MERS), and the Recently emerging severe acute Respiratory syndrome coronavirus 2 are all members of the corona virus family (SARS-CoV-2, the causative agent of the diseases COVID-19).[1] Corona virus primarily causes respiratory syndrome and intestinal infections in animals and humans.[33] The new strain of coronavirus, COVID-19, was first arrived in Wuhan, China, which is in December 2019. The virus has since, spread over the earth. Coronaviruses are a family of viruses that can encourage Respiratory Disorders in humans. The name, "corona" get from means crown-like spikes on the surface of the virus. respiratory syndrome, Middle East respiratory syndrome, and the common cold are some examples of coronaviruses that lead to illness in a human. COVID-19 virus enters in body through the mouth, nose, and eyes (directly from the airborne droplets or from the transfer of the virus from your hands to your face). The virus transfer to the back of your nasal passages and mucous membrane in the back of your throat. It binds to cells there, begins to proliferate, and moves into lung tissue. From there, the virus can diffuse to other body tissues.[2]

The journey and spread of the Novel Corona virus from person to person

COVID-19 is mostly spread:

- When the virus enters in respiratory droplets, if an infected person coughs, sneezes, talks, sings, or breathes near around you (within six feet). This is conception to be the main way COVID-19 is spread.
- When the virus is transmitted in small respiratory droplets that remain in the air for minutes to hours from an infected person who is more than six feet away or has since left the space. This method of spread mostly occurs in enclosed spaces with indigent ventilation.
- From touching and close contact, shaking hands with an infected person.
- By touching surfaces that the virus attack on, then touching your eyes, mouth, or nose before washing your hands.

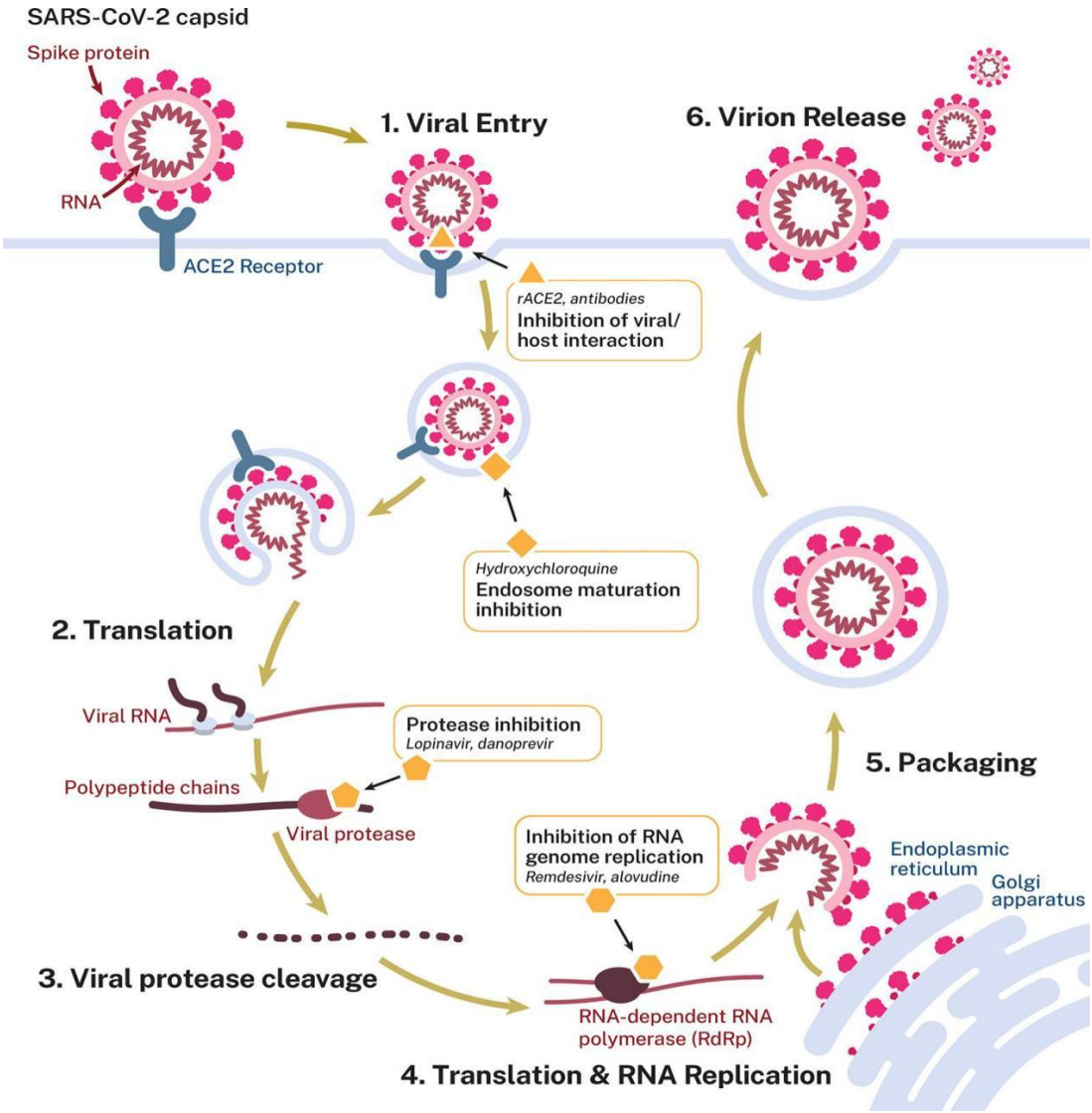

Fig. 1: The Life Process of Sars-Cov-2 In Host Cells.

SARS-CoV-2 principally affects the respiratory tract (nasal epithelial cells, pneumocytes, alveolar macrophages) and the gastrointestinal tract (enterocytes). The entry of virus through direct interaction between the viral 'S' protein and the cellular receptor otensin-converting enzyme. Following enters, the viral genome is released and transported into the viral replicase polyproteins and Polyproteins ab, which are cleaved into functional proteins by viral proteases.[33] The replication of the viral genome is mediated by the viral replication complex, including the RNA-dependent RNA polymerase. Viral nucleocapsids are set up from the packaged viral genomes and translated viral structural proteins and liberate through exocytosis. Potential targets and hypothesize mechanism of action for antiviral actions are shown 1: blocking virus or host cell interaction through the use of antibodies or nanobodies (and convalescent plasma therapy) a recombinant Angiotensin-Converting Enzyme 2 protein; use of hydroxychloroquine (based on in vitro data) to inhibit endosome maturation; use of protease inhibitors to inhibit viral or endosome membrane fusion or viral polypeptide maturation; nucleoside or nucleotide analogs to inhibit viral genome replication.[3] Covid related diseases mostly affect the respiratory, central nervous, digestive, and hepatic systems.[4]

MECHANISM INVOLVE IN CORONAVIRUS DISEASE

COVID-19 is a severe settled infection, and the most normal side effects at the beginning are fever, dry cough, and weariness, mostly with sickness, loose bowels, or other gastrointestinal side effects.[34,35] Most patients may create diffuse alveolar injury, dynamic respiratory disappointment, and acute respiratory disorder like SARS-CoV, the receptor restricting area (RBD) of 'S' protein on the outside of SARS-CoV-2 ties to the Angiotensin-converting enzyme 2 receptors on the cell up the surface to encourage the infection transfer to the host cell; at that stage, infection uncovered its RNA. then, interpretation of RNA replicase, and structures an RNA replicase-transcriptase complex. By the interpretation and replication, the structure of RNA negative strands will be interpreted for the basic proteins

of the infection later. At that point, the adjunctive proteins and RNA in the cytoplasm gather into new favored particles, which are discharged from contaminated cells by exocytosis form to defile different cells. Each defiled cell produces many new viral particles that spread to bronchi, in the long run, arrive at the alveoli, and extrapulmonary organs, causing pneumonia and focused on natural diseases. In any case, the Angiotensin engrossed enzyme 2 receptor isn't just communicated in the respiratory organs. It has been accounted for that, by using the RNA- sequence strategy to communicate ACE2 receptors in human tissues, the quantity of ACE2 receptors communicated in the GIT (high in the throat, small digestive tract, and colon, low in the stomach), kidneys, and testicles is about multiple times higher than that in the lung.[35,36,37] some of may be target organs for SARS-CoV-2 attack. It might elucidate why a few patients with COVID-19 created other framework wounds clinically adjacent to respiratory framework wounds. Besides, it has been founded that SARS COV-2 nucleic corrosive location is certain in the defecation of certain patients, indicating that there might be a live infection in the defecation and the stomach-related structure might be a potential course for COVID-19.[38] The primary pathological dissection of a covid-19 patient revealed extensive alveolar damage and aspiratory hyaline layer organization, both of which are associated with ARDS. SARS and MERS are neurotic signs of the lungs. Stream cytometry meant that the quantity of CD4+ and CD8+ T lymphocytes infringe on blood was immensely diminished, although their state was uncontrolled. Other than this, CCR4+ and CCR6+ Th17 lymphocytes with profoundly proinflammatory impacts widen in CD4+ T lymphocytes, CD8+ T lymphocytes had a high convergence of cytotoxic granules, in which 31.6% were perforin positive, 64.2% were positive, what's more, 30.5% were both molecule lysin and perforin positive. It exhibits that the serious resistant injury in this patient might be firmly connected to the over activation of T lymphocytes informed by the expansion of Th17 lymphocytes and the high cytotoxicity of CD8+ T lymphocytes.[39,40.5]

CHLOROQUINE / HYDROXYCHLOROQUINE

Chloroquine is an antimalarial drug that was proposed in 1934. Chloroquine was first the drug to be evaluated for efficacy against SARS-CoV2 infection with SARS[6] Hydroxychloroquine is an analog of chloroquine, which was proposed in 1946. Hydroxychloroquine is used in the treatment of autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis also in malarial disease.[3] The chloroquine and hydroxychloroquine potentiate the endosomal pH which inhibits fusion of severe acute respiratory syndrome coronavirus and the host cell membranes. Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 receptors, which may interfere with the binding of a severe acute respiratory syndrome associated with coronavirus to the cell receptor. *In vitro* studies have recommended that chloroquine and hydroxychloroquine may block the transport of SARS-CoV-2 from early endosomes to endolysosomes[13] probably preventing the release of the viral genome.

MECHANISM OF ACTION

Chloroquine and Hydroxychloroquine also exhibit the mechanism of action of hydroxychloroquine/chloroquine against SARS-CoV-2 has yet to be fully elucidated.[26] SARS-CoV shares 79% genetic sequence similarity to SARS-CoV-2, but is thought to result in more severe infection with a case mortality rate of 10% vs. 3% for SARS-CoV-2[27,28] on studies initially performed on -CoV, it is believed that SARS-CoV-2 enters cells by binding to the angiotensin-b enzyme 2 (ACE-2) receptor, and that chloroquine may prevent the virus from binding to this receptor which inhibits terminal glycosylation. New research has discovered that the hydroxychloroquine may also prevent SARS-CoV-2[29] from binding with gangliosides, which in turn may inhibit virion contact with the ACE-2 receptor.[30] Both hydroxychloroquine and chloroquine additionally can incorporate into endosomes and lysosomes, resulting in an increased pH of intracellular compartments. These organelles normally require an acidic nature for homeostasis. Eventually, this increase in pH results in their dysfunction, which leads to defective protein degradation, endocytosis, and exocytosis needed for viral infection, replication, and propagation[31] antecedent work has also indicated that coronaviruses can use proteins on the surface of endosomes and endolysosomes for viral entry into host cells.[32,12]

ADVERSE EFFECT

- QTc prolongation
- Torsade de Pointes, ventricular arrhythmia
- Hypokalaemia, Hypoglycaemia
- Retinopathy, Bone marrow suppression

i. FAVIPIRAVIR

Favipiravir contains a chemical change of a pyrazine analog. Favipiravir was discovered and proved to be effective against the influenza virus in vitro for the first time.[14] Favipiravir was approved for pandemic preparedness only, not seasonal influenza treatment. In 2014, the drug was marketed in China as a second-line treatment for new or re-emerging influenza epidemics.[15] Evidence from in vitro, in vivo, and clinical studies strongly suggest that the safety profile and mechanism of action of favipiravir make it a hopeful drug use against a broad spectrum of RNA viruses.[16] Due to the risk of teratogenic effect and embryo toxic nature of favipiravir, a restrictive selling approval with strict regulations has been granted for manufacturing and clinical administration of the agent.[17] Interferon and ribavirin are other available drugs with a wide margin of anti-viral activity. However, unlike favipiravir which is adequately tolerable in humans, interferon and ribavirin have harmful adverse effects that restrict their use in the clinic.[18]

MECHANISM OF ACTION

Favipiravir is a pro-drug which shows its antiviral action after incorporation into infected human cells[19,20] with the infected cells, favipiravir undergoes phosphorylation and further phosphorylation to form an active structure naming favipiravir ribofuranosyl-5′-triphosphate (favipiravir-RTP). The exact antiviral mechanism of favipiravir-RTP has not been yet known. although, there are three hypotheses for the mechanism of action:

a) Misinformation of one or two consecutive favipiravir-RTP into the viral RNA and inhibiting the further RNA extension (chain termination)[21, 22]

b) The binding of the favipiravir-RTP to the active site of RdRp and blocking the enzyme activity[18]

c) Lethal mutagenesis[23]

In the lethal mutagenesis stage, favipiravir-RTP is misin incorporated into a nascent RNA without termination of the RNA replication. Further, RNA cycle synthesis, the regions of the viral genome that has incorporated favipiravir-RTP will be liable to mutagenesis. Favipiravir-RTP serves as a nucleotide and may arbitrarily pair to natural nucleotides cytosine (C) and uracil (U). It may be accountable for a large mutation frequency perceived in the treated viral populations. An excess of mutations ultimately destroys the viruses.[24] In vitro and in vivo data studies suggested that lethal mutagenesis is the most probable favipiravir mechanism of action. although, two distinct studies support the chain termination as the responsible mechanism of action.[25] Favipiravir-resistant viruses could spread when resistance is generated but the probability will depend on the genetic environment of the virus.[1]

ADVERSE EFFECT

- Teratogenic effects occur when the drug is given to pregnant women
- Increased uric acid levels
- Decreased white blood cells count

REMDESVIR

Remdesvir is a small molecule monophosphoramidate prodrug of an adenosine analog. It carries out its action by inhibiting the RNA-dependent RNA-polymerase.[7]

Remdesivir cannot be given by oral administration because the oral route will result in hydrolysis of the prodrug to Nuc-MP in the GI tract.[8] Remdesivir is an investigational drug essentially, used to treat viral infections. It is classified as a broad-spectrum antiviral potential antiviral activity against a variety of RNA viruses. It is used as a primary drug treatment option, and according to Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, remdesivir may be examined as a novel "standard of care" for COVID-19.[5]

MECHANISM OF ACTION

Remdesivir closely resembles adenosine.[9] Remdesivir (GS-5734) to treat against the novel coronavirus by inhibiting replication of the virus in the body.[10] This process takes place by interfering with the novel coronavirus's RNA polymerase, an enzyme needed to copy a DNA sequence into an RNA sequence during the process of transcription.[11] Remdesivir is a prodrug that undergoes modification in the body before becoming an active drug. It is under a class of nucleoside analog, one of the oldest classes of antiviral drugs, and resembles the RNA base adenosine. In general, nucleoside and nucleotide are analogs that simulate the structure of a true nucleoside or nucleotide. The imitated structure may then be incorporated into the virus and in this sense may be considered a "Q" agent with therapeutic benefit.[12] Remdesivir acts by substituting the adenosine analog for the native molecule in the developing RNA strand of the new coronavirus RNA polymerase enzyme that replicates the genetic material. By the introduction of the modified agent remdesivir, replication of the novel coronavirus is fragmented and the virus desists to multiply and is not able to infect more cells in the body.[13]

ADVERSE EFFECT

- Low blood pressure, nausea, vomiting, sweating, shivering.
- Allergic reactions such s shortness of breath, wheezing.
- Destruction of cells in the liver.

Table 1: Pharmacological Property Of Chloroquine, Favipiravir, And Remdesvir.[9]

PROPERTY	HYDROCHLOROQUINE	FAVIPIRAVIR	REMDESVIR
HALF- LIFE TIME	537 hours	2-5.5 hours	20 hours
ROUTE OF ELIMINATION	~40-50 by renally, ~16-21 unchanged, ~25% sloughed off in skin ~24-25% through faeces	Favipiravir metabolites are predominantly renally cleared	~74% eliminated in urine, ~10% is unchanged ~18% eliminated in faeces
ABSORPTION AND CLEARANCE	Absorption in Plasma and distributed in cell, 96 ml/min	The bioavailability of favipiravir is almost complete at 97.6%. The mean Cmax for the recommended dosing schedule of favipiravir is 51.5 µg/ml.	Poor hepatitis stability hence, faster clearance altered administrated via IV
METABOLITES	Desmethylhydroxychloroquine	hydroxylation primarily by aldehyde oxidase and to a lesser extent by xanthine oxidase to the	Triphosphate metabolite

		inactive metabolite	
DRUG INTERACTION	Hydroxychloroquine showed severe drug interaction	showed severe drug interaction with Pyrazinamide, Rapaglinide, Theophylline	Drug interaction not known or not available
TOXICITY	Headache, cardiovascular events, QT Prolongation, conduction disorders, ventricular tachycardia and retinopathy	There is evidence that use during pregnancy may result in harm to the baby. Teratogenicity, Hyperuricemia	Not well reported literature, while Encephalopathy is reported by similar analogues drug

CONCLUSION

By analysing all the studies, it should be concluded that among the drugs Remdesvir plays a crucial role in the treatment novel covid-19, Especially in the treatment of CoV causing severe lung damage. It has been demonstrated to be effective in vitro against SARS-CoV-2, the most effective drug available against SARS-CoV-2. Remdesivir and Favipiravir have shown potent antiviral activities, more efficacious and till date use medicine for COVID-19. Remdesivir is a nucleotide analog prodrug that inhibits SARS-CoV-2. In vitro and in vivo investigations have demonstrated its viral activity against SARs-Cov-2.

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