International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 12, Issue 6, 2020

Review Article

THE POTENTIAL OF REMDESIVIR AGAINST SARS COV 2: A REVIEW

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Received: 12 Jul 2020, Revised and Accepted: 13 Sep 2020

ABSTRACT

Covid 19, the pandemic originated in the Chinese city of Wuhan, had the entire world conquered. The structure and transmission of the causative organism, Coronavirus is well studied. Remdesivir, the product of Gilead pharmaceuticals, was effective against many viral infections, including Ebola and SARS. It comes under the category of nucleoside prodrug and has given promising results in the early trials against SARS COV 19. In depth, research is taking place at a rapid pace, so that Remdesivir will be available to the therapeutic community as an effective remedy for the pandemic caused by SARS COV2. If this meets success, the darkest era in the modern history of mankind may become a memory in the near future.

Keywords: Covid, Remdesivir, Nucleoside, Protide, Virion, Viral replication

DOI: http://dx.doi.org/10.22159/ijcpr.2020v12i6.40298. Journal homepage: https://innovareacademics.in/journals/index.php/ijcpr
Speedy peer review was done as the subject of the manuscript was related with pandemic.

INTRODUCTION

The entire world is reeling under the outbreak of the corona virus. News from across the globe clearly testimonies the conquest of this tiny organism over the entire world. The pandemic which originated in late 2019, in the Chinese city of Wuhan, had it's source identified as a novel corona virus and was named as Severe Acute Respiratory Syndrome (SARS COV 2) [1, 2] In March 2020, the World Health Organisation (WHO) named this infection as Covid 19 [3]. Corona virus belongs to the family *Corona Viridae* which are viral organisms with an envelope. They have single-stranded RNA and generally infects humans and animals [4]. Their infections ranges from common cold to life-threatening infections like MERS (Middle East Respiratory Syndrome) SARS (Severe Acute Respiratory Syndrome) and the recent outbreak Covid 19 [5].

Discovered in the 1960s, the coronavirus was originally thought to be only responsible for mild disease, with strains such as HCoV 229E and HCoV OC43 responsible for the common cold Coronaviruses primarily cause infections of the respiratory tract and GIT in humans [6]. They are known to cause similar infections in animals too. The perception that coronaviruses cause only mild infections changed in 2003 with the outbreak of SARS in 2003 and again with the outbreak of MERS in 2012 [7]. Both were declared as pandemics, by the WHO [8]. These two types of coronaviruses are thought to be emerged from native bat populations, which maintain a broad diversity of coronaviruses, and were transmitted through an intermediate host to humans. The SARS COV 19 also had it's first transmission from bat population and was declared to be a pandemic by WHO in March 2020 after it's origin in Wuhan and reported spread to more than 190 countries [9]. Presently the country with maximum infected population is the United States of America followed by Brazil, and India [10].

The patients infected with covid 19 develops symptoms ranging from mild fever to severe respiratory failure. The disease was presented as asymptomatic in around 35 % of patients. The common symptoms include fever, cough and myalgia. Symptoms like lack of taste, GI disturbances, headache and sputum production were observed in comparatively less frequency. The progression of the disease to acute respiratory distress syndrome typically occurs in elderly patients who often had a previous history of myocardial ailments or chronic diseases like diabetes. A small portion of affected individuals was observed with symptoms related to the nervous system and coagulopathies [11-15].

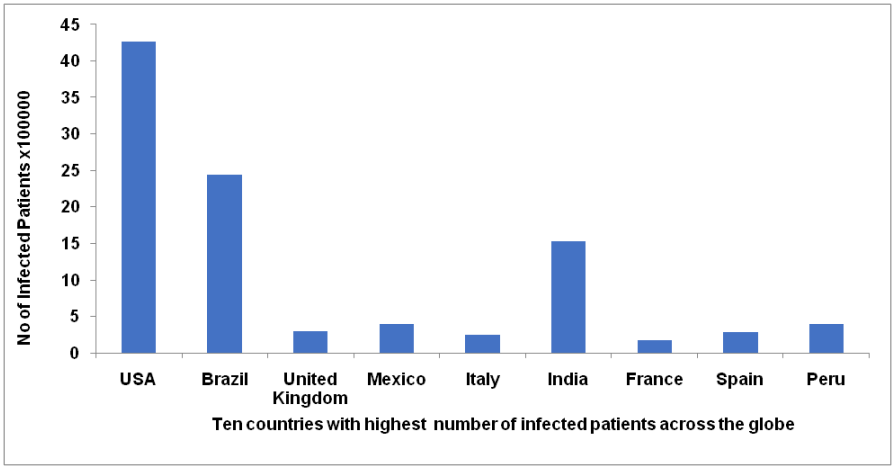

Fig. 1: Number of infected patient's country wise

Virion strucutre of coronavirus

The virion structure of SARS COV 19 is spherical, having a diameter of approximately 125 nm [16]. The club-shaped projections emanate from the virion surface provides the virus the appearance of a solar corona, which prompted the name coronavirus. The nucleocapsid is present inside the viral envelope. Five different proteins play an important role in their mechanism of action. The proteins are Spike protein S, membrane protein M, envelope protein E, nucleocapsid protein N and certain accessory proteins [17]. The S protein helps in binding the virus to the host cell receptor, and also mediates the viral and host cell membranes. The M protein is responsible for maintaining viral integrity [18]. The E protein was known to play a vital role in corona virus assembly. The N protein is responsible for maintaining the nucleo capsid into a helical assembly. The accessory proteins are responsible for viral replication and is also thought to be important for viral-host interactions [19, 20].

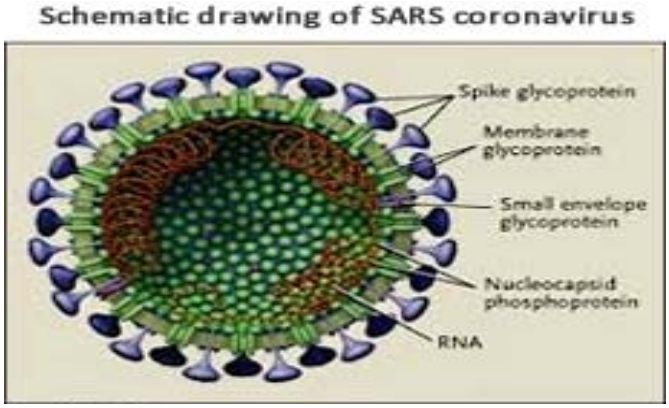

Fig. 2: Virion strucutre of corona virus [21]

Entry of sars cov 19 into host cell

After the virus entry in to the host cell, the translocation of virus in to the host cell endosome takes place. The proteases present in the endosme cleave the S protein is mediating fusion of the membrane. The release of viral genome takes place and the viral protein expression follows. The replication of the viral genome occurs and this is mediated by the viral replication complex. The viral replication complex includes an RNA-dependent RNA polymerase, (RdRp), helicase, exonuclease N and accessory proteins [22, 23].

Remdesivir discovery and introduction as antiviral agent

Remdesivir, the antiviral drug that is thought to be the weapon against SARS COV was patented by Gilead following a collaborative research between Gilead pharmaceuticals, US military and the Centre for Disease Control and Prevention (CDC). The compound GS-5734 was one among the successful candidates, in the screening of more than 1000 compounds against RNA viruses like dengue virus, yellow fever virus, influenza virus, para influenza A and SARS. It produced excellent results when screened for *in vitro* antiviral activity against EBOV during the outbreak of ebola virus infection and has demonstrated its ability aginst a host of corona viruses including SARS, MERS various zoonotic viruses,as well as the circulating human corona viruses HCoV-OC43 and HCoV-229E, causative agents of common cold [24-26].

Remdesivir: chemistry

The molecular formula of remdesivir is C27H35N6O8P and its IUPAC name is 2-ethylbutyl (2*S*)-2-[[[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxy-oxolan-2-yl]methoxy-phenoxyphosphoryl]amino] propanoate [27]. Remdesivir is an analog of the nucleoside adenosine and designed as a prodrug [28]. Drug latentiation is necessitated by the poor cell permeability of the nucleosides. Generally, antiviral drugs that are nucleoside analogs are modified into their monophosphate, ester or phophoramidate forms. These modifications increase the cellular permeability and once it crosses the cell membrane to be inside the cell, it is biotransformed to the nucleoside or nucleoside monophosphate form [29].

The unique structural feature in remdesivir is the cyano group at the 1’ position of ribose, and is expected to prevent the molecule from binding to the host mitochondrial RNA. The comparative stability of the cyano group during cellular activation can be attributed to the strong nucleophilic C-C bond. The phosphoramido group provides enhanced lipophilicity to the molecule. The phenoxy group attached to phosphorus aids in improved lipophilicity and consequent cell permeability [30, 31].

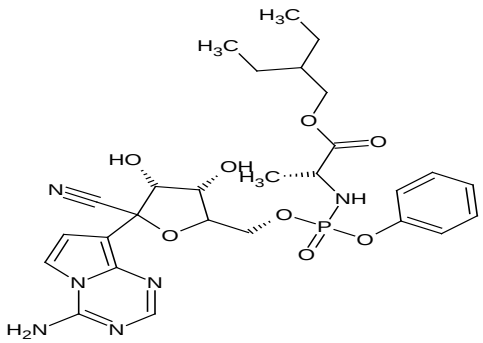

Fig. 3: Chemical structure of remdesivir

Mechanism ofaction of remdesivir

The mode of action of remdesivir is delayed chain termination of viral RNA synthesis [32]. This termination is not spontaneous, but occurs after the addition of 3-5 nucleotide bases to the viral RNA chain. The active metabolite of remdesivir, the triphosphorylated form is structurally similar to adenosine tri phosphate (ATP). This tri phosphorylated form inhibits the activity of viral RNA dependent RNA polymerase (RdRp) in the infected cells. Remdesivir triphophate with the 3’ hydroxyl group can form the phospho diester bond for chain elongation, but the chain elongation is terminated after the addition of 3-5 nucleotide bases to the viral RNA [33]. The under lying molecular mechanism for the chain termination is the steric influence of 1’ cyano group present in remdesivir. The cyano group makes steric interaction with the serine residue S861 [34]. An additional mechanism of action is the inhibition of viral exonucleases responsible for the proofreading of nucleoside anti metabolites by the newly synthesized RNA [35, 36]. This sequence of metabolic conversations is represented in fig.

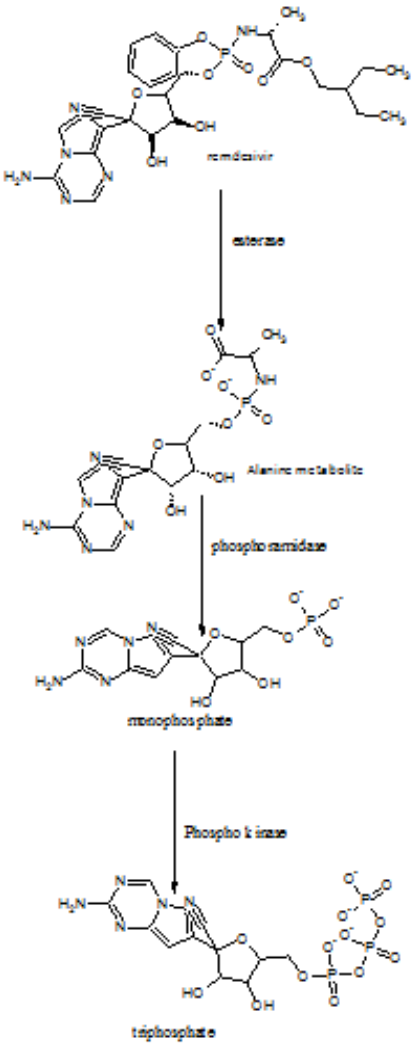

Fig. 4: Metabolic conversion of remdesivir to remdesivir triphosphate

Remdesivir is designed to be the prodrug of nucleotide monophosphate. Such prodrugs are termed protides [37]. The nucleotide monophosphate is linked to a phosphoramidite ester with a phenyl group. This modification renders the monophosphates highly lipophilic. Remdesivir penetrates into the intra cellular compartment and by the action of the enzyme esterase, undergo molecular cleavage to form the carboxylate [38]. The carboxylate undergoes cyclization, then it loses the phenyl group and gets transformed into an alanine metabolite. The enzyme phosphoramidase cleaves the phosphorus-nitrogen bond to leave the carboxyl amino group so as to regenerate the monophosphate. It then undergoes diphosphorylation to become the triphosphate. The triphosphate form binds to RdRp to terminate chain elongation [39].

Pharmacokinetics of remdesivir

Remdesivir is widely distributed across the tissues like bladder, liver, kidney, prostrate gland, salivary gland and pancreas. It is distributed aas well in the seminal vesicles, epidymis and testes. The unbound fraction is about 12.1%. Remdesivir poorly crosses the blood-brain barrier. The major route of elimination is renal (63%), whereas biliary excretion accounts for 27% [40-43].

CONCLUSION

The pandemic covid 19 has created irrecoverable damage to global health and economy. Governments, scientists, drug research groups and pharmaceutical organizations across the globe are taking great efforts for the discovery of an effective agent to eradicate covid 19. Simultaneously the efforts to redirect the existing the therapeutic agents for the treatment of covid 19 is also under progress. Remdesivir, the nucleoside analogue has been introduced in to clinical practice successfully for the treatment of viral infections. The *in vitro* and *in vivo* screening of remdesivir has yielded promising results. The results of the ongoing clinical trials are expected to be published shortly and if the data pertaining to the clinical trials are promising, it can be concluded that the darkest era in the modern history of the human race may come to an end.

ACKNOWLEDGEMENT

The author acknowledges the support of the management, St. Joseph's College of Pharmacy, Cherthala, Kerala, India for the support.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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