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AN OVERVIEW OF REMDESIVIR EFFECT AGAINST NOVEL CORONA VIRUS

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ABSTRACT

Recently the largest war in front of the world is to fight against the Novel coronavirus. Which cause by severe acute respiratory syndrome (SARs CoV-2). It's big challenge in front of researchers and developing company to prepare drug and vaccine in very short duration of time. In that situation use of other convenient and therapeutic drug is another option useful against covid-19 in 2016 after some clinical trials it is concluded that remdesivir is fully effective against corona virus. After several clinical trials and cell culture study it is establish that remdesivir is an antiviral drug therapeutic effect against covid-19. This virus replication take place by using genetic material with the help of enzyme called as RNA dependent RNA polymerase (RdRp). So Remdesivir is a prodrug of an adenosine -C nucleoside analogue. When remdesivir is enter into body, respiratory epithelial cell in human it gets metabolize by phosphorylation and convert into nucleoside triphosphate as an active form. This active form acts on RdRp and inhibit replication of virus. But knowledge about potency and efficacy of remdesivir therapy to treat Covid -19 and has been limited. Recently WHO said that remdesivir does not show therapeutic effect against Covid-19 and no effect on mortality rate. So, use of remdesivir is restricted in all over India. The basic purpose behind the study of an overview of remdesivir in covid-19 is to understand remdesivir and its pharmacological against viral infection.

KEYWORD: SARs-CoV-2, remdesivir, drug interaction to body, pharmacokinetic, adverse effect.

INTRODUCTION

The new outbreak of Novel coronavirus (Covid-19) was first identified in December 2019 at Wuhan city in china.[1] Coronavirus causes various types of severe syndrome in animals and humans.[2] The severe acute respiratory syndrome (SARs-CoV–2) and the Middle East respiratory syndrome (MERs-CoV–2) are one of them the causative agent of Covid-19.[3] SARs-CoV-2 classified into Beta genera which previously name as 2019 Novel Coronavirus (2019-n CoV), another Human Corona virus 2019 (HCoV-19) and due to bat virus its name as Rhinolophus.[2] There are mainly six species of HCoV -19 out of which one species subdivided into two different strains and making seven strain of HCoV -19 together.[2,3] WHO officially name the Corona virus as pandemics on 11 March 2020.[4] Fever, cough, tiredness is the primary symptom of Covid-19 as there is increase in infection sore throat, diarrhoea, conjunctivitis, headache, loss of taste or smells, Rashes on the skin and there with discoloration of figures and toys development, the most severe symptoms include difficulty in breathing, chest pain and pressure pneumonia, loss of speech movement.[4,5] When healthy persons come in contact of infected person, the virus spread by through frees in atmosphere at a while it gets soak up by normal or healthy persons. Then after entry of virus into the host cell via specific receptor and from fusion with the cell membrane, they started to replicate using virus RNA dependent RNA polymerase (RdRp). [6] This single-stranded RNA polymer is a highly protected amount difference strain, making the drug target site.[7]

SARs-CoV-2: This type of virus belongs to the subfamily-*Orthocoronavirinae*, family-*Coronaviridae*, order-*Nidovirales*.[8] Generally virus particle is 80 to 160 mm in diameter and SARs -CoV-2 genome is 26 kb to 32 kb in length that is largest RNA single-stranded RNA Virus.[9] This RNA genome had a 5' head and 3' polyadenylated tail structure. The Corona virus consist of spike protein(S), nucleoprotein(N), polyprotein(P) and membrane protein(M) with 4,2,22 variation level of amino acids.[10] It's also contained six Open Reading Frames (ORFs) out of which first open reading frame close to the 5' terminal and fusion with 16 nonstructural protein (nsp1-16). Mainly this nsp 1-16 responsible replication of virus and remaining ORFs fused with S, N, P protein. However, eight subtype of protein such as C3a, 3b, p6, 7a, 7b, 8b, 9b and ORF14 are responsible for assembling of viral particles.[11,12,13]

Spike(S) protein of HCoV-19 bind to Angiotensin Converting Enzyme-2 (ACE2) receptor with help of transmembrane protease, serine 2(TMPRSS2) enzyme. This ACE2 present in lung, kidney, Gastric track. [14,15, 16] Viral protein S, E, M then transmission into the endoplasmic reticulum (ER). Replication of viral protein take place in Endoplasmic Reticulum-Golgi Intermediate Comportment (ERGIC) and new mature virion form and laterally release of mature virion into body which shown in Fig.1[16] Some of virion encode with plasma membrane, this virion replicated the gene with the help of two polyprotein that is PP1a and PP1ab. [15,16] Generally PP1a and PP1ab consist of non-structural protein(nsps) and that functional role in intracellular replication. This polyprotein divided in to form individual nsps with help of enzyme protease such as papain like protease (PLpro) and serine type protease. Many of nsps then assembling to form replicase transcriptase complex (RTC).[16]

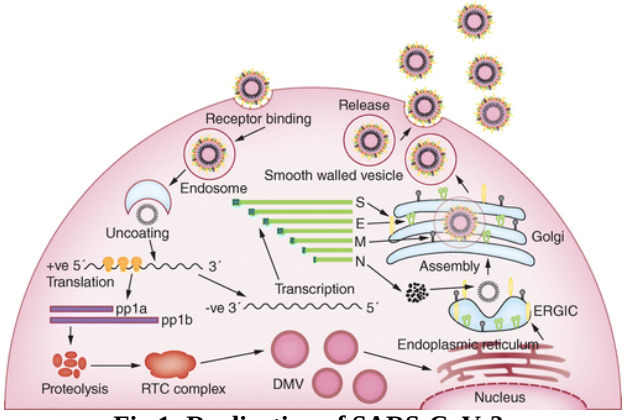


Fig 1: Replication of SARS-CoV-2.

The purpose of using antiviral drug to inhibit RNA dependent RNA polymerase so that nucleoside and nucleotide containing analogues is proffered. example acyclovir which is guanine analogue used for treatment of herpes virus. Zidovudine is nucleo base used as a drug of choice for HIV infected patient. [8,17] In between 2013 to 2016 Ebola virus is outbreak in west Africa, after some clinical study research a prophesied that remdesivir effective as antiviral drug used to treat Ebola virus. [18] However, during Ebola outbreak remdesivir does not show effective in point in randomized clinical trials. [19] So, nowadays this remdesivir again used for fight against novel corona viral infection.

Remdesivir: Trade name veklury is a derivative of adenosine nucleoside analog and developed by U. S biopharmaceutical company Gilead science. They are used to treat such type of viral infection like as Ebolavirus, param paramyxoviruses, Nipa virus and newly in 2020 FDA approved remdesivir effective against COVID-19

Synonyms: GS-5734, RDV, GS5734, Veklury

Chemical formula: C27H35N6O8P

Chemical weight: 602.585mg

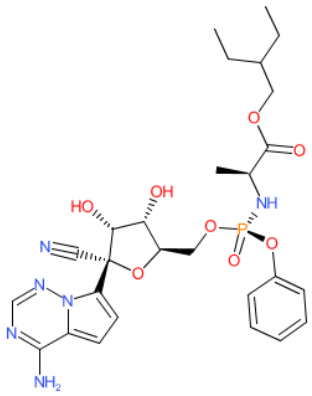
Chemical name : 2-ethylbutyl N - (2S)-2-{[(S)-{[(2R,3S,4R,5R)-5-{4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl}-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy}(phenoxy)phosphoryl]amino}propanoate.

Class- Broad spectrum antiviral drug.

Compound type: synthetic organic

Active form: GS-441524

Route of administration: Intravenous



Drug interaction to body: The target for antiviral drug is viral enzyme or attack of viral replication point of host, such target site is RNA dependent RNA polymerase (RdRp). [20,21] In addition to antiviral activity that inhibit the nucleoside and nucleotide and prevent the RNA synthesis.[22] Remdesivir is a prodrug of adenosine c nucleoside analog, that under goes intracellular metabolism to for remdesivir triphosphate (GS-443902) as active form.[23] As related to other antiviral drug the form of (GS-443902) is targeting effective for replication of corona virus RNA material. This adenosine analog is effective compound that act by come across with endogenous natural RNA nucleoside. In case of Ebolavirus, remdesivir show targeting and therapeutic effect to inhibit viral RNA replication.[24] The suggested target active site in Ebolavirus is RdRp, however (GS-443902) triphosphate it's act as substrate for RdRp.[25]

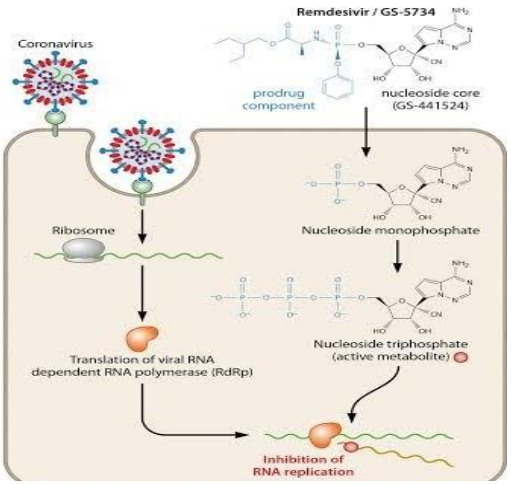


Fig 2: Drug interaction.

Remdesivir is competition with ATP for replication of new strand at RdRp binding site. Amalgamation of GS-

443902 causes chain termination at 5th position. Ebolavirus and SARs CoV -2 both are RNA virus. So, in case of coronavirus remdesivir restrict with replication of SARs-CoV and MERs-CoV by prolong chain termination at 3rd poison. Which result inhibition of RNA replication.[26] For the process of transcription and translation the untimely termination of RNA synthesis is inhibited by GS-443902 and this effect are determined using cell-based model.[27] Remdesivir (GS-5734) lead to intracellular activation with inhibition of coronavirus replication. From the passage where prodrug component attaches to nucleoside core to from GS-441524.whenever GS-441524 undergo phosphorylation and to form Active remdesivir triphosphate (GS-443902) that act on RdRp and inhibit viral RNA replication.[28]

Pharmacokinetic

- Absorption: Pharmacokinetics is studied by giving the multiple dose of remdesivir through intravenous route in case of severe patients, to determine absorption pattern. [25] In 2019 controlled clinical study is done for the treatment of coronavirus cases where loading dose is 200 mg which is followed by the 100 mg of maintenance dose for 5 to 10 days. This dose shows good effect in healthy volunteers which shows in Fig.3. Remdesivir is preferred to given intravenously not by the orally due to its hepatic metabolism.[29]

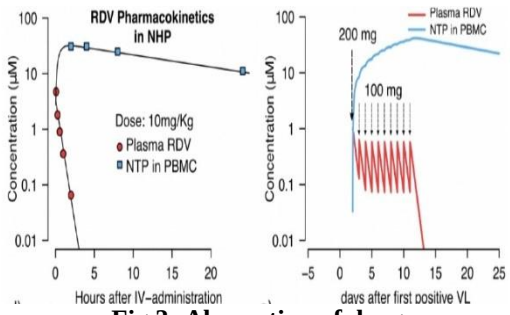


Fig 3: Absorption of drug.

- Distribution: Remdesivir binding is varies in all species. 80 –90.6% of remdesivir bound to plasma protein in human. [30] It has 8.0 % protein binding fraction in rat and 14.2 % in cynomolgus monkey.
- Metabolism: Remdesivir it is a prodrug which are metabolized into GS –441524, further it undergoes phosphorylation nucleoside monophosphate derivative and finally form active nucleoside triphosphate which inhibit RNA-dependent RNA polymerase enzyme and prevent viral multiplication which shown in Fig.4.[31] The nucleoside analogue that is GS – 5734, which enters into the cell and it is rate limiting step. [25]

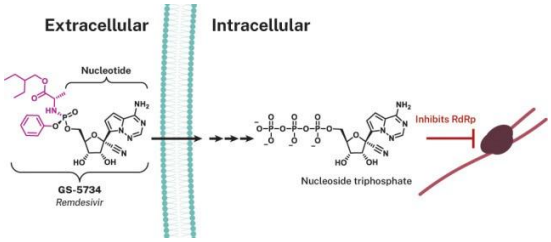


Fig.4: Metabolism of drug.

- Execrations: In Rats and monkey the elimination occur preferably by renal and biliary excretion and 74 % of remdesivir is converted into faeces and 18% in urine. Generally, 49% dose of remdesivir is recovered in urine. [29] Safety of remdesivir in individual having in individual having GFR less than 30 ml /min, during treatment of 5 to 10 days. [32]
- Drug interaction: In vitro study it was defined that remdesivir is a substrate for CYP3A4, CYP2C8, CYP2D6, OAPT1Bi (organic anion transporting polypeptides 1Bi (OAPT1Bi) and p–gp (p – glycoprotein transporters)[25,32] Remdesivir is inhibitor for CYP3A4, CYP2C8, CYP2D6, OATP1B3, BSEP (bile salt export pump) MRP4 (multidrug resistance protein 4) NTCP (sodium /taurocholate co-transporting polypeptide).[21,25]

Clinical study: To determine safety and efficacy of a drug clinical trials is achieved, which involve randomized, double-blind placebo-controlled trial. There are 1062 patient nominated for clinical study (randomized), out of them 541 have treated with remdesivir and 521 with placebo remdesivir administered by IV 200 mg loading dose with 100 mg of maintenance dose. Remdesivir treated patient have rapid recovery time than placebo.[1,7] In Washington on 19 Jan 2020 there is one case found that 35-year-old man suffering from cough and fever after checking (RTPCR) test it observed that he has affected by covid-19 so doctor treated patient with remdesivir. Later that remdesivir was given to 7 severe hospitalized patients in USA. It's showing better therapeutic effect. Beigel and colleagues performed a clinical trial in that it's observed that there is short recovery time for remdesivir administered patient than that of placebo (median recovery time 11 to 15 day).[33]

Adverse Effect: As per guideline describe by experts the use of remedsivir is limited. But the negligence of drug usage there are several types of adverse effect found in patients like that hepatotoxicity, gastro-intestinal symptoms, respiratory toxicity, nephrotoxicity, cardiovascular toxicity, reproductive toxicity etc. And other like high alanine transaminase level, high aspartate transaminase level, high amount of bilirubin in blood, nausea, fever.[34,35]

CONCLUSION

Remedsivir is one of the best emergency drugs in case of Covid-19. But some adverse effect shown in patient WHO suspends drug. Because they did trials with 7000 counties across globe and found no evidence of improvement in ill patients or Covid related patients, besides the low and middle income countries like India witnessed rise in Covid cases and the demand for remdesivir was more and to satisfy the demand they had to increase the supply and this resulted in rise in remdesivir prices hence WHO first warned the countries to stop using remdesivir and then after the 7000 patients trial they suspended the remdesivir as it was against their treatment guidelines.

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