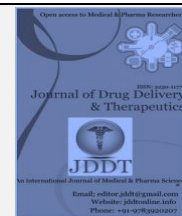
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Review Article

Remdesivir for COVID-19: A review of pharmacology, mechanism of action, in-vitro activity and clinical use based on available case studies

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Abstract

Remdesivir as a drug attracted a very serious consideration of whole Globe in treatment of the pandemic disease COVID-19. More recently published in-vitro inhibition activity and in-vivo case studies were showing promising clinical results and outcome of effective inhibition of SARS-CoV-2 virus by the use of remdesivir. However at the same time, use of the remdesivir showed substantial detrimental adverse events in patients which needs a special attention during treatment course of COVID-19. Thus, the use of remdesivir in treatment of COVID-19 is having current international interest although some more clinical evidences are still necessary in order to understand the actual efficiency and mechanism of remdesivir against COVID-19. In view of this, the present literature study spotlight the current ongoing research related to use of remdesivir which includes (i) pharmacology of remdesivir, (ii) mechanism of action of remdesivir (iii) in-vitro inhibition of remdesivir against SARS-CoV-2 virus, (iv) in-vivo analysis and clinical use of remdesivir against COVID-19. Finally possible adverse events (of use of remdesivir) are also discussed considering the pharmacovigilance concern.

Keywords: Remdesivir; COVID-19; Remdesivir side effects, Remdesivir pharmacology; SARS-CoV-2 virus

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1. Introduction:

COVID-19 is the acronym that is used for the novel coronavirus disease-2019, which is caused due to newly emerging delta-coronavirus named as SARS-CoV-2 [1-3]. The first case of COVID-19 was appeared in December 2019 in Wuhan city of Hubei province china and by February 2020, it is declared as global pandemic with the public health emergency due to its more contagious nature than that of SARS-CoV and MERS-CoV [2,3]. As of now (11th July 2020), approximately 126,16,579 confirmed cases have been reported in almost 215 Nations with 5,62,039 fatalities throughout the World [4]. Research related to COVID-19 is still going on regarding to exact origin, transmission, clinical

features, mechanism of infectivity and use of drug to cure COVID-19 [1-3]. Till date various significant breakthroughs have been reported in literature regarding to (i) COVID-19 clinical manifestation, (ii) genetic sequence with phylogenetic relationship of SARS-CoV-2 virus and (iii) possible in-vitro-prohibition of SARS-CoV-2 virus by various available chemical drugs [5]. However, till date no drug is approved by FDA to use against COVID-19 treatment, while most of the drugs are used on the basis of drug repurposing theory to treat COVID-19 [1,3]. Further, research related to development of vaccine is going on high priority which may take almost 18 months (or more) to design first effective and safe vaccine against COVID-19 [3]. Since, majority of vaccines

for the COVID- 19 are in clinical trial phase which is a time consuming protocol to develop a successful vaccine [3].

More recently, FDA has issued an emergency-use-authorization of an undergoing investigational antiviral agent remdesivir for the treatment of hospitalized patients of COVID-19 with disease severity. [6-8]. Thus the use of the remdesivir drug in the treatment of COVID-19 possess great international interest at present, although collective consensus has not been attained yet which may need more scientific data, clinical trails outcome and evidences in order to prove the efficacy of the remdesivir against COVID-19 [9]. In view of this, the present review article is aimed to highlight (i) the antiviral use to remdesivir against various viral diseases (ii) possible mechanism of remdesivir against viral infection, (iii) in-vitro inhibition of SARS-CoV-2 virus by remdesivir (iv) recent scenario of use of remdesivir against COVID-19 based on available case studies/ clinical trials and (v) pharmacovigilance concerns about use of remdesivir.

2. Remdesivir pharmacokinetics and use of remdesivir as an anti-viral agent:

Remdesivir is developed by GILEAD pharmaceutical in 2009 to treat the hepatitis, which displayed poor to moderate anti-viral potency against hepatitis [10,11]. Further research literature reported anti-viral use of remdesivir against various coronaviruses such MERS-CoV, SARS-CoV, δ -coronaviruses family [12-16] hepatitis C virus [17], nipah [18], marburg [19], enterovirus [20], Filo-, Pneumo-, and

Paramyxo-viruses [21] etc. Remdesivir was re-pitched by the Gilead Pharmaceuticals for treatment of Ebola in 2014 which displayed efficient activity against the Ebola virus and used widely against Ebola virus epidemic [22,23]. Further in recent scenario, remdesivir is used to treat against COVID-19 which may have possesses side effects. Besides this, remdesivir may be considered as a safer drug than that of hydroxychloroquine since, half life of remdesivir is much less as compared to that of hydroxychloroquine (Table 1, entry 1) [23,24]. Almost 21 % hydroxychloroquine in body remained unchanged while that of remdesivir is just only 10 % (Table 1, entry 2) [24-27]. Remdesivir showed faster clearance due to its poor hepatic stability and hence recommended via IV administration (Table 1, entry 3) [28-30]. Remdesivir showed less harmful metabolites (triphosphate) than that of hydroxychloroquine (desethylhydroxychloroquine) (Table 1, entry 4) [15,23,28]. Drug interaction and various detrimental side effects are very well known about hydroxychloroquine which involves the headache, cardiovascular events, QT prolongation, conduction disorders, ventricular tachycardia and retinopathy etc (Table 1, entries 5,6) [1,24,27]. However, side effects of the remdesivir are not well known/available except to that of encephalopathy which is shown by acyclovir a nucleoside analogue similar to that of remdesivir [31]. More recently, the FDA Emergency Use Authorization suggests a loading dose of 200 mg (5 mg/kg) once in a day in patients \geq 40 kg and 100 mg from day 2 (2.5 mg/kg) [26].

Table 1: Pharmacological properties of hydroxychloroquine and remdesivir

Property	Hydroxychloroquine	Remdesivir
Half-life time	537 hours [24]	20 hours [23]
Route of elimination	~40-50% by renally, ~16-21% unchanged, ~2.5% sloughed off in skin ~24-25% through feces [24,25]	~74% eliminated in urine, ~10% is unchanged, ~18% eliminated in feces [26,27]
Absorption and clearance	Absorption in Plasma and distributed in cell [24, 28], 96 mL/min [29]	Poor hepatitis stability, hence faster clearance after administrated via IV [30]
Metabolites	Desethylhydroxychloroquine [28]	Triphosphate metabolite [15,23]
Drug interaction	Hydroxychloroquine showed severe drug interaction [1,24]	Drug interaction not known or not available [27]
Toxicity	Headache, cardiovascular events, QT prolongation, conduction disorders, ventricular tachycardia and retinopathy etc. [1]	Not well reported in literature, while Encephalopathy is reported by similar analogues drug [31]

3. Remdesivir as a pro-drug and chemistry:

Remdesivir GS-5734 and GS-441524 are the pro-drug and nucleotide analogue, works by inhibiting the basic viral RNA replication process inside the host-cell and causes termination of virus reproduction with subsequent reduction of viral load inside the patient body [32-35]. Remdesivir (GS-5734) is highly specialized inactive form of molecule, because of its structural resemblance with human nucleotide it acts as a pro-drug of actual remdesivir (GS-441524). This

remdesivir (GS-5734) is primarily metabolite into remdesivir (GS-441524). Thus, the pro-drug remdesivir (GS-5734) is administered in an inactive form wherein it go through different series of enzymatic reaction (esterase, kinase, amidase and phosphotase etc.) which causes the structural modifications and leads to produce active form triphosphate nucleotide as well remdesivir (GS-441524) [33-35]. Figure 1 depicts the series of reactions from inactive pro-drug remdesivir (GS-5734) to active drug remdesivir (GS-441524) [34,35].

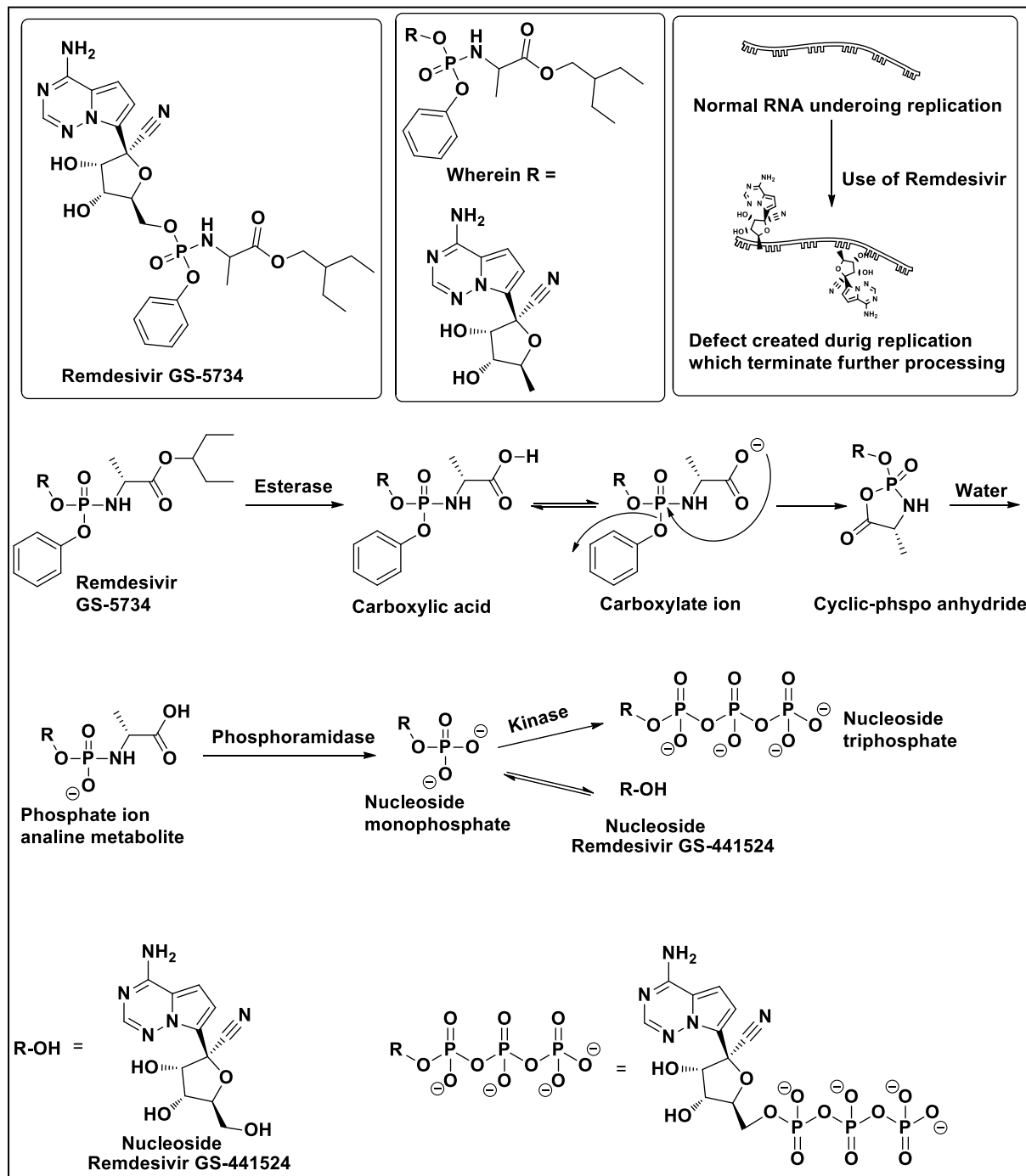


Figure 1: Possible mechanism of action and chemistry of remdesivir as an anti-viral

- (i) Initially, ester group get hydrolyzed by esterase enzyme leads to produce carboxylic acid derivative and corresponding carboxylate ion [32-35].
- (ii) This carboxylate ion attacks on phosphorous group and leads to form cyclic phosphor-anhydride with release of phenoxide ion [32-35].
- (iii) Then cyclic phosphor-anhydride ring get open into the phosphate ion alanine metabolite [32-35].
- (iv) Finally, this alanine metabolite is get hydrolyzed and get converted into the nucleoside monophosphate by reaction of enzyme phosphoramidase [32-35].
- (v) This nucleoside monophosphate gets converted into the nucleoside triphosphate and nucleoside analogue GS-441524 acts as an active metabolite which incorporated in the anti-viral mechanism which is a

modified nucleo-base similar to that of adenosine [32-35].

Thus cyto-chemistry and enzyme catalyst plays a very important role to get an actual active form of the remdesivir inside the cell which cannot diffuse back to outside [32,33]. The presence alkyl group and phenyl group modification increases the lipophilicity of drug which increases the speed of transfer of molecules from extracellular to intracellular [33]. Further this pro-drug molecule remdesivir (GS-5734) easily metabolized into active form remdesivir (GS-441524) once it enters into intercellular medium and shows its anti-viral action [35].

4. Remdesivir and its possible mechanism of action:

Remdesivir is closely resemble to adenosine [32-35]. The active form of drug metabolite is nucleoside triphosphate remdesivir and remdesivir (GS-441524) which is available in

the cytoplasm [32] after metabolism and unable to diffuse back to extracellular medium. This active form remdesivir (available in cytoplasm) is utilized by the cell viral RNA dependent RNA polymerase instead of the adenosine during the process of viral genetic material replication which is incorporated into the growing viral genetic strand instead of adenosine [34,35]. This incorporation in the viral genetic material not only stops the replication process but also unable to repair viral genetic materials [33,34].

It is well identified that, lung is the most affected organ in coronavirus disease [1,2]. In lungs the type II alveolar cells contains large number of ACE-2 (angiotensin-converting enzyme-2) which acts as recognized receptors wherein the spike (S) protein of the SARS-CoV-2 binds [36]. Further, density of the ACE-2 receptor may vary from organ to organ and hence it may be possible that, SARS-CoV-2 virus may display its infection ability in the gastrointestinal tract, gastric glandular cells, duodenal, rectal epithelium cells, Leydig cells, renal tubular cells, seminiferous ducts also wherein ACE-2 expression present [37-39]. Moreover Fan et al., [39] reported that, gastrointestinal tract, kidney and testis may causes damage after SARS-CoV-2 infection due to presence of ACE-2 expression. However, Warren et al., [23] reported that, remdesivir distributed and absorbed easily in testes and epididymis immediately after four hours of administration [23,27]. These two facts suggested that, remdesivir can be effective against the SARS-CoV-2 virus as it may inhibit the virus replication inside the cell organ wherein SARS-CoV-2 receptor ACE-2 expression is available. Thus the present supporting literature evidences propose

theoretical effectiveness of the remdesivir in the COVID-19 treatment [40].

5. In-vitro inhibition of SARS-CoV-2:

Recently various reports are available which are summarized in table 2 (entry 1-14) for in-vitro inhibition of coronavirus (SARS-CoV-virus, MERS-CoV-virus, HCoV-OC43-virus, HCoV-229E-virus and SARS-CoV-2-virus) by remdesivir. In-vitro inhibition of the remdesivir against SARS-CoV-2 virus is very well documented in the FDA document (Table 2, entries 1-3) [26]. Further European Medicine Agency also documented the in-vitro efficacy of the remdesivir against SARS-CoV-2 virus (Table 2, entries 4) [41]. Choy et al., [42] reported EC50 value of 23.15 μM against SARS-CoV-2 virus (Table 2, entries 5) [42]. Wang et al., mentioned EC50 value of 0.77 μM with the selectivity index (SI) of 129 against SARS-CoV-2 virus (Table 2, entries 6) [43]. However, Sheahan et al., [44] reported the IC50 value of 0.069 μM and 0.074 μM for SARS and MERS coronaviruses (Table 2, entries 7,8) [44]. Further, Sheahan et al., [12] mentioned EC50 value of 8 μM for the MERS coronaviruses (Table 2, entry 9) [12]. Other researchers (Brown et al., [45] and Agostini et al., [14]) also demonstrated that, remdesivir shows inhibitory effect against various coronaviruses (Table 2, entries 10-12) [14,45]. Pruijssers et al., [46] observed EC50 value of 0.01 μM while, Wang et al., [47] found EC50 value of 0.46 $\mu\text{g/mL}$ for the inhibitory effect of remdesivir against the SARS-CoV-2 virus (Table 2, entries 13,14). Thus the in-vitro analysis study supports possible therapeutic use of remdesivir against the SARS-CoV-2 virus infection (COVID-19).

Table 2: In-vitro inhibition of coronavirus by remdesivir

Entry	Virus	Cell line	EC50	IC50	CC50	SI	Ref.
1	SARS-CoV-2	HAE cell	9.9 nm	---	---	---	26
2	SARS-CoV-2	HAE cell	137 nm	---	---	---	26
3	SARS-CoV-2	HAE cell	48 nm	---	---	---	26
4	SARS-CoV-2	Vero cell	0.137 μM	---	---	---	41
5	SARS-CoV-2	Vero cell	23.15 μM	---	>100 μM	---	42
6	SARS-CoV-2	Vero cell	0.770 μM	---	>100 μM	129.8	43
7	SARS-CoV	HAE cell	---	0.069 μM	---	---	44
8	MERS-CoV	HAE cell	---	0.074 μM	---	---	44
9	MERS-CoV	Vero cell	8 μM	---	---	---	12
10	HCoV-OC43	Huh 7	0.15 μM	---	>100 μM	67	45
11	HCoV-229E	Huh 7	0.024 μM	---	>10 μM	68	45
12	SARS-CoV	Calu-3	1.10 μM	---	300 μM	250	14
13	SARS-CoV-2	Vero cell	0.010 μM	---	---	---	46
14	SARS-CoV-2	Vero cell	0.460 $\mu\text{g/mL}$	---	---	---	47

6. In-vivo inhibition of SARS CoV-2:

Considering the in-vitro analysis it can be possible to use remdesivir against COVID-19. Very few case studies are available which displayed the role of remdesivir in COVID-19 treatment. Wang et al., [47] studied use of remdesivir in adults having severe COVID-19 symptoms in which clinical improvement is not observed by use of remdesivir. In this case 102/158 (66%) patients showed adverse effects by use of remdesivir than that of 50/79 (64%) patients in control group. Thus the remdesivir did not show better use and

improvement may be due to aged (median age 65 years) COVID-19 patients (Table 3, entry 1) [47]. Grein et al., [48] mentioned compassionate use of remdesivir against COVID-19 in which 36 (68%) patients showed clinical benefits, 8 (15%) patients showed worsen condition, while 7 (13%) patients were died. (Table 3, entry 2) [48]. Beigel et al., [49] reported preliminary observation for use of remdesivir against COVID-19. In this study, patient given remdesivir were recovered in 9-12 days than that of control patients which were recovered in 13-19 days. Mortality rate was

7.1% in studied remdesivir group than that of 11.9% in control group [49]. Adverse events were noted in 21.1. % patients administered with remdesivir, than that to 27.8% patients in control (Table 3, entry 3). Goldman et al., [50] proposed use of remdesivir for 5 or 10 days in COVID-19 patients in which clinical improvement has been observed by use of remdesivir in 64% patients (5 day group) and 54% patients (10 day group) along with some normal adverse events (Table 3, entry 4). Other than this Hillaker et al., [51] and Kujawski et al., [52] also used remdesivir against COVID-

19, however there sample size is too small to judge the exact clinical outcome of use of remdesivir in treatment of COVID-19. Moreover, various clinical trials are ongoing [53]. Thus from the available case studies, one can predicted that, remdesivir can work effectively in early phase of disease in treatment of COVID-19 however, its use may be restricted by some common side effects which are under investigational study. The large number of studies and confirmed outcome can be expected for use remdesivir against COVID-19 in coming days.

Table 3: In-vivo use of remdesivir in treatment of COVID-19

Study	Study design	Treatment and Dosage	Control	Observation and general conclusion	publish/pre-print	Ref
1	Randomised, double blind, placebo controlled. N = 237; TD = 28 days; MA= 65 RN =NCT04257656	158 patient: Remdesivir 200mg on day1 and 100 mg from second to tenth day. + supplementary medicine	79 Patient: Placebo infusion + supplementary medicine	Clinical improvement is not observed by use of remdesivir in patients of COVID-19. 102/158 (66%) patients showed adverse effects by use of remdesivir than that of 50/79 (64%) patients in control group. Remdesivir did not show better use and improvement in adults as mean age is 65.	Published	Wang et al., [47]
2	Observational Study Non-controlled N = 61; MA= > 18 TD = 28 days	Out of 61 patients 53 were given remdesivir 200mg on day1 and 100 mg from second to tenth day.	0	36 (68%) patients showed clinical benefits, 8 (15%) patients showed worsen condition, while 7 (13%) patients were died.	Published	Grein et al., [48]
3	Randomised, Double blind, placebo controlled. N = 1063; TD = 14 days; Age group= 58.9±15.0 RN= NCT04280705	541 patient: Remdesivir 200mg on day1 and 100 mg from second to tenth day. + supplementary medicine	522 Patient: placebo infusion + supplementary medicine	Patients given remdesivir were recovered 9-12 days than that of control patients which are recovered in 13-19 days. Mortality rate was 7.1% in remdesivir group than that of 11.9% in control group. Adverse events were noted in 21.1. % remdesivir group, than that to 27.8% patients in control	Published	Beigel et al., [49]
4	Randomized, open label clinical trial Estimated Number= 397; MA= > 18 TD = 14 days RN =NCT04292899	Group A (5 days) 200 patients and Group B (10 days) 197 patients: Standard therapy + remdesivir 200mg on day 1 and 100 mg for remaining days as per group.	0	Clinical improvement by use of remdesivir has been observed in 64% patients (5 day group) and 54% patients (10 day group). Side effects were nausea (in 9% of patients), worsening of respiratory problems (in 8% patients), increased alanine aminotransferase level (in 7%patients) and constipation (in 7% patients).	Published	Goldmann [50]

N = Number of populations (patients), MA = median age in population (years), TD = Treatment days, RN = Registration Number

7. Prophylactic use and side effect of remdesivir:

Very few reports are available for the proposed prophylactic use of remdesivir against COVID-19. European medicine agency documented the prophylactic use of remdesivir which reduces the viral load significantly [41]. Sheahan et al., [15] and de Wit et al., [13] proposed that, prophylactic use of the remdesivir may prevent the physiological defect occurred due to SARS-CoV-2 infection. Agostini et al., [14] also reported the prophylactic efficacy of remdesivir against various coronavirus diseases. Thus from the available literature it may be possible that, remdesivir showed its effective prophylactic and therapeutic use against COVID-19. However, more evidences are still awaiting in order to understand the efficient prophylactic use of remdesivir against COVID-19. Further, it is noteworthy to mention adverse influence of remdesivir in present medical emergency scenario. Goldman et al., [50] noted adverse events of use of remdesivir which involves the nausea (in 9% patients), worsening or respiratory failure (in 8% patients), increased alanine aminotransferase level (in 7% patients), and constipation (in 7% patients). Beigel et al., [49] reported anemia (in 7.9% patients than 9.0% of control group); pyrexia (in 5.0% patients than 3% of control group); hyperglycemia (in 4.1% patient than 3% of control group) and increased aminotransferase. Grein et al., [48] reported adverse events in 60 % patents during treatment which involves the increased liver enzymes, diarrhea, renal impairment, and hypotension, while 23 % patients showed severe adverse effects such as multiple-organ-dysfunctioning, septic shock, kidney injury. Wang et al., [47] also reported common side effects in use of remdesivir which involves constipation, hypo-albuminaemia, anaemia, thrombocytopenia, and elevated bilirubin. Thus the use of remdesivir may have severe side effects hence use of the remdesivir should be administrated only under medical supervision.

8. Conclusion:

In conclusion, remdesivir pro-drug (GS-5734) can be effectively used in the treatment of viral infections. Use of this pro-drug essentially offers active form remdesivir (GS-441524) metabolites into the cytoplasm. This metabolite interfere the RNA replication process of the SARS-CoV-2 virus via incorporation in the viral genetic material synthesis process and stops the reproduction of new virus particles. Furthermore, in-vitro analysis study showed significant reduction of the viral load by use of remdesivir which supports the therapeutic use of remdesivir against the SARS-CoV-2 virus infection. In-vivo analysis also demonstrated the significant role of the remdesivir in treatment COVID-19 with some adverse events. However prophylactic use of the remdesivir needs some more attention in therapeutic use. Thus the use of remdesivir against COVID-19 is having great international interest which needs further more supporting evidences to use remdesivir efficiently in common practicing to cure COVID-19.

Note for readers: Readers must refer cited research article(s) for more detail information. Clinical treatment should NOT be given based on this review article.

Conflict of interest: None

Ethical clearance: Not required

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