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The Efficacy of Remdesivir in Reducing SARS-CoV-2 Viral Load and Its Safety on COVID-19 Patients: A Systematic Review

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Abstract

Background: This study aimed to examine the effectiveness of Remdesivir in reducing Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) viral load and its safety for antiviral therapy in Coronavirus disease 2019 (COVID-19) treatment.

Methods: This systematic review used data sources from the PubMed, ProQuest, SpringerLink, and ClinicalTrial.gov databases for relevant observational and interventional studies during August 2020 to August 2021. Studies evaluating Remdesivir in adults hospitalized for COVID-19 were included in this review. This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines.

Results This review found 9 studies that were relevant to the study objectives. In total, 1,088 patients participated as subjects. Three studies demonstrated the effect of remdesivir in reducing SARS-CoV-2 viral load in upper and lower respiratory tract specimens. Six studies demonstrated that remdesivir was safe for use in a variety of baseline conditions (patients on hemodialysis and patients receiving kidney transplantation), had no significant hepatotoxicity, did not increase the risk of acute kidney injury, and did not increase eGFR or systemic symptoms in patients taking remdesivir.

Conclusion: Remdesivir has been shown to reduce SARS-CoV-2 viral load and was safe for use as antiviral therapy in the treatment of COVID-19, but an assessment of randomized controlled trial for the effect of Remdesivir on viral load reduction was not available yet. *(J Respirol Indones 2022; 42(1): 76-85)*

Keywords: COVID-19, remdesivir, SARS-CoV-2 viral load, safety, systematic review

Pengaruh Remdesivir dalam Menurunkan *Viral Load* SARS-CoV-2 dan Keamanannya pada Pasien COVID-19: Tinjauan Sistematis

Abstrak

Latar belakang: Penelitian ini bertujuan menilai efektivitas remdesivir terhadap penurunan viral load dari Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) dan keamanannya sebagai terapi antivirus pada pengobatan Coronavirus disease 2019 (COVID-19).

Metode: Tinjauan sistematis ini menggunakan data yang bersumber dari pangkalan data Pubmed, ProQuest, SpringerLink, dan ClinicalTrial.gov untuk uji observasional dan intervensional yang relevan selama Agustus 2020 hingga Agustus 2021. Penelitian yang mengevaluasi remdesivir pada pasien dewasa yang dirawat di rumah sakit karena COVID- 19 diikutkan dalam tinjauan ini. Tinjauan sistematis ini mengikuti panduan penulisan Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

Hasil: Ada 9 penelitian yang relevan dengan tujuan penelitian ditemukan. Total terdapat 1.088 pasien yang turut serta sebagai subjek penelitian. Tiga penelitian menunjukkan efek remdesivir dalam menurunkan viral load SARS-CoV-2 pada spesimen saluran pernapasan atas dan bawah. Enam penelitian membuktikan remdesivir aman digunakan pada berbagai kondisi dasar (pasien dalam hemodialisis dan pasien penerima transplantasi ginjal), tidak memiliki hepatotoksisitas yang bermakna, tidak meningkatkan risiko acute kidney injury, dan tidak meningkatkan eGFR atau gejala sistemik pada pasien yang menggunakan remdesivir.

Kesimpulan: Remdesivir telah terbukti menurunkan viral load SARS-CoV-2 dan aman digunakan sebagai terapi antivirus pada pengobatan COVID-19, namun belum ada penilaian dari uji acak terkontrol mengenai efek remdesivir terhadap penurunan viral load. *(J Respirol Indones 2022; 42(1): 79-85)*

Kata Kunci: COVID-19, remdesivir, viral load SARS-CoV-2, keamanan, tinjauan sistematis

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INTRODUCTION

Since the emergence of COVID-19 as a worldwide outbreak, the World Health Organization (WHO) issued an emergency use authorization (EUA) regarding antiviral therapy which could be used in this condition. One of the antivirus was remdesivir (RDV).[1]

Remdesivir (also known as GS-5734) is a nucleoside analogue which acts by inhibiting RNA-dependent RNA polymerase that has previously been used to treat SARS (Severe Acute Respiratory Syndrome) and MERS (Middle East Respiratory Syndrome) which are structurally similar to COVID-19.[2]

To find out the increase in COVID-19 cases, measuring the viral load is one of the strategies. Viral load quantification is very useful for evaluating severity of infection, predicting the evolution of viral infection and its recurrence.[3]

In an in vitro study, RDV was able to inhibit the SARS-CoV-2 replication.[4] Research conducted on Vero E6 Cells showed that RDV was able to reduce infectious viruses (EC_{50} = 23.15μM) and to reduce viral RNA copies ((EC_{50} = 26.90 μM).[5] Treatment of RDV in a Ces1c-/- hDPP4 mouse model infected with MERS-CoV was found to decrease the viral load.[6]

A study conducted on rhesus macaques demonstrated that RDV reduced viral titration in bronchoalveolar lavage after 12 hours from the first administration of RDV, and reduced pulmonary viral load after 7 days of therapy. This study also demonstrated that lung damage in animals receiving RDV therapy was reduced, and supported an early initiation of RDV treatment in COVID-19 patients to prevent pneumonia.[7,8]

In this systematic review we reviewed recent sources to determine the effectiveness of using RDV with SARS-CoV-2 viral load measurement. Given that there is no gold standard yet in the COVID-19 treatment, and RDV is still categorized as EUA by WHO, it is necessary to conduct a new study on the safety of using RDV.

METHOD

Search Strategy

Reporting of this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline.[9] Literature searches were carried out systematically through the ProQuest, PubMed, SpingerLink, and ClinicalTrials.gov databases.

The literature search strategy is detailed in e-Tables 1, 2, and 3 on the Supplementary data. The research publication year was limited from August 2020 to August 2021. the search for literature sources was not limited to English.

Literature screening was conducted independently by AF and RR. First, we identified the duplicated literature and excluded them. Once there were no duplicated literatures, title and/or abstract screening was performed. Titles and/or abstracts which were not relevant to the desired result; and not RCT, Cohort, or Case-control studies were excluded. Furthermore, the full text of the study would be reviewed and selected for qualitative analysis. Disagreements among investigators would be resolved by consensus, and if necessary, consultation with a third investigator (RS).

Inclusion criteria

Observational and interventional studies included were studies that discussed the effectiveness of RDV by measurement of SARS-CoV-2 viral load and/or safety of RDV therapy compared with other antiviral therapies, placebo, or standard of care (SoC) therapies for COVID-19. The criteria for positive COVID-19 patients were evidenced by the RT-PCR results, were hospitalized, and were≥18 years old.

Exclusion criteria

The exclusion criteria were duplicate studies, review articles, meeting abstracts, case reports, case series, letters and editorials, brief communication, in vitro and in vivo studies, and studies without original information on RDV therapy.

Data extraction

Data on the author's name, study design, number of patients, duration of illness before RDV use, inclusion criteria, groups or subgroups of patients, viral load measurements and safety were extracted.

Risk of bias assessment

We used the Newcastle-Ottawa Scale[10] to assess the risk of bias in observational study. The researchers independently assessed the risk of bias with the tool, and then other researchers re-examined them.

RESULTS

From 1478 studies identified through database searches (ProQuest: 648; PubMed: 370; SpringerLink: 452; ClinicalTrial.gov: 8), about 22 full-text articles were selected. After matching our eligibility criteria, 9 relevant observational studies were included in this review for qualitative analysis (Figure 1). Complete data from the qualitatively analyzed studies are shown in Table 1.

Viral Load

Measurement of the SARS-CoV-2 viral load in 86 patients in South Korea was performed at three-time points, namely between days 1–5, between days 6-10, and between days 11–15 of hospital admission (HA). It used the upper and lower respiratory tract specimens. To measure viral load reduction, changes in C_T value of the RNA-dependent RNA polymerase gene were evaluated on day 15 of hospital admission in both groups (RDV vs. SoC). Analysis of upper respiratory tract specimens in the RDV group showed significantly higher C_T values (n=46; median=1.33; interquartile range [IQR]=0.62-1.33) compared to the SoC group (n=35; median=0.80; IQR=0.19-1.13; P=0.043).[11]

On the lower respiratory tract analysis, the RDV group also showed a higher increase in C_T values (n=33; median=0.99; IQR=0.26-1.15) compared to the SoC group (n=28; median=0.75; IQR= -0.05 - 0.99) but the difference was not significant (P=0.291).[11] Evaluation of viral load reduction using RT-PCR-tested upper respiratory tract specimens at each time point (HA 1-5, 6-10, and 11-15) were selected and compared. Slope C_T values were significantly higher in the RDV group (mean, 5.10±3.08) than in the SoC group (mean, 2.68±3.63; P = 0.007).
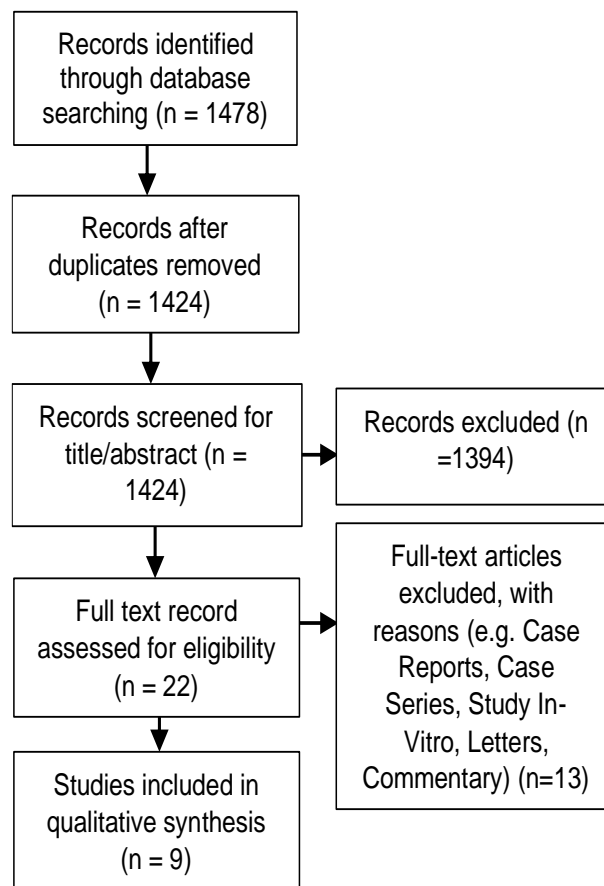
Figure 1. Flow Chart of PRISMA

The increase in C_T values from HA 1-5 to 11–15 was also significantly higher in the RDV group (n=32; mean=10.19±6.16) than the SoC group (n=28; mean=5.36±7.27; P=0.007).[11]

Results on lower respiratory tract specimens pointed that the slope of the increase in C_T values was higher in the RDV group (n=21; mean=4.54±3.93) than in the SoC group (n=21; mean=2.97±3.36), but not statistically significant (P=0.170). The RDV group demonstrated a higher increase in C_T values from HA days 1-5 to days 11-15 (mean, 9.02±7.84) compared to the SoC group (mean, 5.94±6.72), but the difference was not significant (P=0.179).[11]

Table 1. The study design and the measured outcome of the included studies

Authors (years)	Type of Study	Selected details of study design and participants	Group 1 sample size	Group 2 sample size	Median duration of illness before RDV therapy	Outcome
VIRAL LOAD						
Joo, et al. (2021)	Cohort study	Severe Illness Group 1: RDV Group Group 2: Supportive care group	48	38	7.42 days	Slope of C_T values ($P = 0.043$); median (IQR): - RDV= 1.33 (0.62–1.33) - Supportive care= 0.80 (0.19–1.13) Difference in changes of C_T values from days 1–5 to days 11–15 ($P = 0.007$); mean: - RDV= 10.19±6.16 - Supportive care= 5.36±7.27
Goldberg, et al. (2021)	Observational study	Severe COVID-19 Group 1: RDV Group 2: Control	29	113	Not mentioned	a. First point to end point, decrease (%) ($P=0.7349$): RDV: 13.8% Control: 11.5% b. First point to mid-point ($P=0.1120$) RDV: 31% Control: 17.7% c. Mid-point to end point ($P=0.588$): RDV: 24.1%, Control: 29.2%
Barratt-Due, et al. (2021)	Clinical study	Group 1: RDV + SoC Group 2: SoC	42	57	7.4 days	Viral load, Log10 count/1000 cells (SD): Group 1: 1.6 (1.6) Group 2 2: 2.3 (1.8) Measurements were carried out on days 3–5, 7–9, and then every 3 days
SAFETY						
Aiswarya, et al. (2021)	Observational, prospective study	Moderate or severe illness -	48	-	3 days (IQR, 2-4 days)	1. Acute coronary syndrome = 1 patient 2. Worsening of behavioral disorder = 1 patient
Kalligeros, et al. (2020)	Phase 3, Clinical trial	Group 1: RDV Group 2: Supportive care	99	125	6 days (IQR, 3-8 days)	1. AKI; patients (%) - stage 1: 14 (54) - stage 3: 12 (46) 2. AST increase; patients (%) - Grade 1: 35(100) 3. ALT increase; patients (%) - Grade 1: 31(100) 4. Serum total bilirubin increase; patients (%) - Grade 1: 8(50) - Grade 2: 5 (31) - Grade 3:3 (19)
Buxeda, et al. (2021)	Cohort study	-	51	-	3 days (IQR, 2–5 days)	1. AKI: 11.7% 2. T-cell mediated rejection: 1 patient 3. Another patient presented thrombotic microangiopathy

Authors (years)	Type of Study	Selected details of study design and participants	Group 1 sample size	Group 2 sample size	Median duration of illness before RDV therapy	Outcome
Falcão, et al. (2021)	Cohort study	Group 1: Hydroxychloroquine Group 2: RDV	101	48	Not mentioned	Hepatobiliary disorders; patients (%): 4 (8.3%) Acute renal failure:1 (2.1%) Nervous system disorders: 1 (2.1%) Other disorders: 1 (2.1%)
Garcia-Vidal, et al. (2021)	Cohort study	Group 1: RDV Group 2: Control	123	119	7 days (4–9 IQR)	No adverse events requiring remdesivir discontinuation were reported
Biancalana, et al. (2021)	Observational, retrospective study	Group 1: RDV Group 2: Control	80	29	Not mentioned	Very small percentage developed AKI

An Israeli study involving 142 patients comparing viral load reductions in the RDV vs control group found that the viral load measurement decreased by 13.8% vs 11.5% (P=0.7349) from the first point to the last point; 31% vs 17.7% (P=0.112) from the first point to midpoint; and 24.1% vs 29.2% (P=0.588) from midpoint to the endpoint. Patients receiving RDV therapy were found to have slightly lower viral loads than those not receiving this therapy in the first trial, although the difference was not significant (26.8±7.05 vs 25.67±6.02, P=0.36). This difference remained insignificant when the final tests of the two groups were compared (33.94±5.22 vs 32.54±5.78, P=0.109).[12]

Early administration of RDV (< first 7 days after symptom onset) could significantly increase clinical improvement. The study showed that within a median of 11 days after symptom onset and receiving RDV therapy, 37 of 196 (19%) patients no longer had detectable viral RNA on nasopharyngeal and oropharynx swabs.[13,18]

A study using oropharyngeal swab specimens showed viral load measurements of log10/1000 cells (SD) in the RDV group and the SoC group of 1.6 (1.6) vs 2.3 (1.8). The viral load measurements between the two groups were not significantly different but the group of patients taking RDV generated lower measurements results.[13]

Safety

A study conducted on 48 dialysis patients found that the use of RDV in COVID-19 patients had no immediate adverse effects. One patient experienced acute coronary syndrome, 6 hours after the first dose of RDV. One patient experienced worsening behavior after 15 hours of RDV use. Patients >50 years old had a significant decrease in serum ferritin (P = 0.005). Six patients with elevated serum ALT levels at admission were not observed to have worsened due to RDV therapy (P = 0.35).[14] In this study, there was no control group, so adverse events were only explained based on findings without comparison, which was a source of bias in this study (Table 2).

Another cohort study with 99 subjects taking RDV obtained that there were 14 subjects with stage 1 acute kidney injury (AKI) and 12 subjects with stage 3 AKI.

There were 35 subjects who had elevated aspartate aminotransferase (AST) grade 1 and 31 subjects experienced increase in alanine aminotransferase (ALT). The increase in total serum bilirubin grade 1 was experienced by 8 patients, 5 patients in grade 2, and 3 patients in grade 3. The incidence of AKI, transaminitis, and hyperbilirubinemia occurred in the RDV group and the supportive care group was not significantly different (AKI, P=0.12; increased AST, P=0.20; increased ALT, P=0.25; increase in total serum bilirubin, P=0.94).[15]

A study of 51 kidney transplant recipients who used RDV as COVID-19 treatment found that AKI occurred in 27.7% of patients. Most were stage 1 AKI (57.1%) and only 1% required renal replacement

therapy (RRT). Of the 14 recipients who had AKI, increase in SCr prior to the initiation of RDV was demonstrated by 8 recipients, therefore, renal dysfunction could not be attributed to drug use. AKI after RDV initiation occurred in 11.7% of subjects. No subject required discontinuation of RDV therapy due to renal impairment. RDV was well tolerated, so there were no significant safety concerns with drug administration.[16]

The study included 48 subjects taking RDV known to have comorbid diseases (cardiovascular disease, asthma, pulmonary disease, cancer, liver disease, kidney disease, diabetes and HIV). In this study 102 adverse drug reactions (ADRs) were identified. The mean time to ADR was 3.9 days, with onset from day 2 and day 7. Hepatobiliary disorders were identified in RDV therapy, as identified in 4 (8.3%) subjects, while acute renal failure was identified in 1 (2.1%) subject, nervous system disorders occurred in 1 (2.1%) subject, and other disorders occurred in 1 (2.1%) subject. The incidence of ADR was significantly higher (47.5%) in hydroxychloroquine (as the comparison group in this study) than in RDV (12.5%) ($P<0.001$).[17]

A study conducted in Spain with 123 subjects stated that RDV was used in four subjects with chronic kidney disease and 24 subjects with reduced immunity (13 with solid neoplasms, 8 with hematological disease and 3 with HIV infection). Median baseline creatinine (IQR) was 0.86 mg/dL (0.72–1.08); but 6 subjects had creatinine values >1.5 mg/dL (1.52 to 1.75 mg/dL) when the RDV was used.

All patients were discharged with creatinine values <1.40 mg/dL (0.84 to 1.40 mg/dL). One subject with an initial creatinine value of 1.39 mg/dL, was discharged with a value of 1.72 mg/dL. Median values (IQR) of initial AST and ALT (before starting RDV) were 39 (24–64) U/L and 36 (23–61) U/L, respectively, while the median values at discharge were 33 (19–57) U/L and 60 (35–97) U/L. The median (IQR) lymphocyte count at baseline and at discharge were 1 (0.8–1.3) x10^9/L and 1.7 (1.2–2.2) x10^9/L, respectively.

No adverse events requiring discontinuation of RDV were reported in this study.[18]

Table *2*. Risk of bias assessment with Newcastle-Ottawa scale

| Author (years) | Selection | | | | Compara bility | Outcome | | | Total |
	Represent ativeness	Selection of the Non-Exposed Cohort	Ascertainm ent of Exposure	Demonstr ation		Assessment of Outcome	Follow -up	Adequacy of Follow-up	
Joo, et al. (2021)	B*	A*	A*	A*	A*	B*	A*	A*	8
Goldberg, et al. (2021)	B*	A*	A*	A*	A*	B*	A*	B*	8
Barratt-Due, et al. (2021)	A*	A*	A*	A*	A*	A*	A*	B*	8
Aiswarya, et al. (2021)	A*	NA	A*	A*	NA	D	A*	B*	5
Kalligeros, et al. (2020)	B*	A*	A*	A*	A*	D	A*	A*	7
Buxeda, et al. (2021)	A*	A*	A*	A*	A*	A*	A*	A*	8
Falcão, et al. (2021)	B*	C	A*	A*	B*	B*	A*	A*	7
Garcia-Vidal, et al. (2021)	A*	A*	A*	A*	A*	B*	A*	A*	8
Biancalana, et al. (2021)	B*	A*	A*	A*	A*	B*	A*	A*	8

Note: NA=Not Available. A, B, C, D are the answers to each question of the Newcastle-Ottawa scale. A star (*) is given to answer A and B. The Stars are count to produce a total score. In general, a study with greater total score has lesser risk of bias.

A study of 80 subjects taking the RDV found that the estimated glomerular filtration rate (eGFR) in the living patients was 81.0±7.4 and the eGFR in deceased patients was 87.8±6. Clinical use of RDV is associated with increased eGFR. In elderly patients who died, the decline in renal function at hospital admission was inversely related to the value of C-reactive protein (CRP). CRP is the most widely used indicator of inflammation to predict disease severity in COVID-19 patients. This confirms the possibility of impaired renal function due to systemic inflammation or due to more severe viral infection.[19]

DISCUSSION

Remdesivir: an introduction

RDV is a broad-spectrum antiviral that exhibits antiviral activity in cell culture and animal models against SARS-CoV, MERS-CoV, and SARS-CoV-2.[20] RDV is administered intravenously in a single dose of 200 mg on the first day. A dose of 100 mg every 24 hours is given from the second day to 5 or 10 days.[21,22] This drug is a prodrug with molecular formula $C_{27}H_{35}N_6O_8P$ and an exact mass of 602.23 Da. In the body, RDV is converted into an active molecule known as GS-441524, with the molecular formula $C_{12}H_{13}N_5O_4$ (291.10 Da).[23] The effectiveness and safety of RDV for COVID-19 have not been established. On May 1, 2020, the US Food and Drug Administration (USFDA) issued an EUA for the use of RDV as the treatment of hospitalized severe COVID-19 patients.[24]

Remdesivir and SARS-CoV-2 viral load

In a study conducted in New York, it was observed that viral load was associated with the duration and severity of symptoms.[25] Viral load and mortality had a significant correlation.[26] Severity of respiratory disease, increased markers of inflammation, increased risk of death, and lower absolute lymphocyte counts were associated with higher viral load.[27] Decreased lymphocytes were known to indicate a risk of developing more severe disease.[28]

The decrease in viral load was also associated with timing of the first administration of RDV. It is known that the spread of SARS-CoV-2 from the respiratory tract reaches its peak on day 2–3 from the onset of clinical symptoms. Early administration of drugs could shorten the length of stay in the hospital, lower the need for mechanical ventilation, and the results of nasopharyngeal and oropharyngeal swabs could also be less detectable.[18]

Studies have shown that RDV was effective in reducing the viral load of SARS-CoV-2. This may be related to its mechanism of action as a nucleoside analogue under research which acts as a competitive inhibitor of viral RNA-dependent RNA polymerase (RdRp).[29] The reduction in SARS-CoV-2 viral load in the tested patients was also accompanied by lower mortality, clinical improvement, shorter hospital stays, and lower intubation rates, which are in agreement with the previously described theory.[12] Patients requiring mechanical ventilation prior to day 28 of hospitalization were less and the duration of mechanical ventilation was shorter in patients using RDV.[11] These findings supported the clinical efficacy of RDV treatment for COVID-19 patients.

Safety of remdesivir

Side effects of RDV can be divided into hepatotoxicity, gastrointestinal symptoms, respiratory toxicity, cardiovascular toxicity, nephrotoxicity, and reproductive toxicity.[30] The most common side effects are diarrhea, rash, AKI, hypotension, anorexia, nausea, vomiting, elevated aminotransferases or bilirubin, and worsening cardiopulmonary status.[31,32]

A review of 6 studies showed that the use of RDV caused acute coronary syndrome and behavioral deterioration.[14] The use of RDV also caused AKI, elevated AST and ALT, and elevated total serum bilirubin, but there were no significant differences between RDV and supportive care groups. Thus, it could not be concluded that the incident was due to RDV.[15] T-cell mediated rejection and thrombotic microangiopathy were also known to occur with RDV.[16]

Hepatobiliary disorders, acute renal failure, and nervous system disorders had also been reported in the studies we reviewed. Overall, the side

effects that occurred in patients taking RDV were not significantly different from the control group, supportive care, placebo or other therapies used as comparison.[19]

Patients who took the RDV >48 hours from admission showed longer time to discharge (12.5 vs 22.5 days from admission), which suggested that earlier treatment might be associated with better clinical outcomes.[16] From the various studies reviewed in this study it was obtained that RDV did not worsen renal function in elderly individuals with and without CKD. Some patients demonstrated a relevant increase in eGFR during RDV administration, this trend seemed to be related to the possibility of recovery from SARS CoV-2 and a better prognosis.[19]

This review found no RCTs. There have been few studies on the effectiveness of remdesivir in reducing viral load and none using an RCT design. The abstract of this paper was presented at the 16th APRU Multi-Hazards Symposium 2021 organized by Disaster Risk Reduction Center Universitas Indonesia in collaboration with Association of Pacific Rim Universities.

CONCLUSION

Remdesivir was effective in reducing viral load, although in some studies there were no significant reductions between remdesivir and control groups. The therapeutic efficacy of remdesivir could be determined by the reduction of SARS-CoV-2 viral load. In addition, information on the reduction in the SARS-CoV-2 viral load could be used to determine the extent of its spread. Remdesivir has been proven safe for COVID-19 therapy because it did not worsen CKD, did not cause AKI, did not increase the level of AST, ALT, and total serum bilirubin, and did not exhibit gastrointestinal disturbances, rash, and hypotension in patients. The safety of remdesivir therapy should be monitored as long as the gold standard for COVID-19 therapy has not been established.

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