Drug Monograph – Remdesivir

Brand Name: VEKLURY®

Generic Name: remdesivir

Manufacturer[1]: Gilead Sciences, Inc.

Drug Class[1]: Antiviral agent

Uses[1,2,3]:

Labeled: For the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) requiring hospitalization

Unlabeled: None

Mechanism of Action[1,2,3,4]: Remdesivir is an inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication.

Pharmacokinetics[1,4,5]:

T_{max}	0.67-0.68 hours
V_d	No data
$t_{1/2}$	~1 hour
Clearance	Not reported
Protein binding	88% to 93.6%
Bioavailability	Not reported

Metabolism[1]: Remdesivir is a phosphoramidate prodrug that must be metabolized within host cells to its triphosphate metabolite to be therapeutically active. It is a CYP3A4 substrate, and a possible CYP2D6, CYP2C8, OAT1b1, and P-gp substrate

Elimination[1]: Remdesivir is 10% eliminated in the urine and has undetectable elimination in the feces.

Efficacy:

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med*. 2020;383(19):1813-1826.

Study Design: Multicenter, double-blind, randomized, phase 3, placebo-controlled trial

Description of Study:

Methods: 1,062 adult patients who were hospitalized with Covid-19 and had evidence of lower respiratory tract infections (LRTI) were randomly assigned (1:1) to receive either remdesivir 200 mg loading dose on day 1, followed by 100 mg daily 9 more days (n=541) or placebo for 10 days (n=521). The main outcome measure was the time to recovery, defined as the first day, during the 28 days after enrollment, on an eight-category ordinal scale, which ranged from 1 to 8 (with 1 = not hospitalized and no limitations on activity, 8 = death). Patients were also assessed on the National Early Warning Score that ranged from 0 to 20 with a higher score meaning increased clinical risk during their hospitalization, from day 1 to day 29.

Outcome Results: In the remdesivir group, patients had a shorter time to recovery versus the placebo group (P<0.001). In the patients with severe disease, the median time to recovery was 11 days versus 18 days in the placebo group. Patients with a baseline ordinal score of 5 had the largest rate ratio (RR) for recovery (RR=1.45). The RR was 1.29 for patients with a baseline ordinal score of 4 and 1.09 for patients with baseline score of 6. For patients receiving mechanical ventilation or ECMO at enrollment (who had a baseline ordinal score of 7), RR for recovery was 0.98. Patients who underwent randomization during the first 10 days after the onset of symptoms had an RR of 1.37, whereas patients who underwent randomization more than 10 days after the onset of symptoms had an RR of 1.20. The odds of improvement in the ordinal scale score were higher in the remdesivir group, as determined by a proportional odds model at the day 15 visit, than in the placebo group (OR for improvement, 1.5). For the as-treated population, serious AEs occurred in 131 of 532 patients (24.6%) in the remdesivir group and in 163 of 516 patients (31.6%). On or before day 29, 273 patients (51.3%) in the remdesivir group and in 295 (57.2%) in the placebo group experienced Grade 3 or 4 adverse events.

Limitations: The initial primary outcome was changed to a key secondary outcome upon the recommendation of trial statisticians in order to make time to recovery the primary outcome. The change was said to be made in response to developing information that Covid-19 had a more protracted course than previously thought. A shortage of matching placebos occurred at some sites such that normal saline was used in its place. This situation could have affected blinding.

Conclusion: The data in the study showed that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 who had evidence of LRTI. However, there was a high mortality rate even with the use of remdesivir. This makes it clear that treatment with an antiviral drug alone is not likely to be sufficient for all patients. More studies need to be conducted to assess which combination of medications are needed to continue to improve outcomes in patients with Covid-19.

Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med*. 2020;383(19):1827-1837.

Study Design: Multicenter, randomized, open-label, phase 3 trial

Description of Study:

Methods: 397 adult patients who were hospitalized with SARS-CoV-2 infection, oxygen saturation ≤ 94% while breathing ambient air, and radiologic evidence of pneumonia were enrolled in this study. They were randomized (1:1) to receive IV remdesivir for either 5 or 10 days. All patients received 200 mg of remdesivir on day 1 and 100 mg once daily on subsequent days. Patients were assessed daily through a physical examination, respiratory status, AEs, and concomitant medications. On trial days 1, 3, 5, 8, 10, and 14, blood samples were taken to test for complete blood count and measurement of creatinine, glucose, total bilirubin, and liver aminotransferases. The clinical status of patients was assessed daily on a 7-point ordinal scale (1 = death; 2 = hospitalized & receiving invasive mechanical ventilation or ECMO… 6 = hospitalized, requiring neither supplemental oxygen nor ongoing medical care; and 7 = not hospitalized. The lowest score from each day was recorded.

Outcome Results:
In this study, 65% of patients who received a 5-day course of remdesivir showed a clinical improvement of at least 2 points on the 7-point ordinal scale at day 14 vs. 54% of patients receiving the 10-day course. After adjustment differences in baseline characteristics, the clinical status at day 14 was similar between the 10-day and 5-day courses (P=0.14). Median duration of hospitalization among patients discharged on or before day 14 was 7 days (IQR, 6 to 10) for the 5-day group and 8 days (IQR, 5 to 10) for the 10-day group. Discharge rates were higher in the overall population among patients who had had symptoms for less than 10 days before receiving the first dose of remdesivir (62% of patients) than among those who had symptoms for 10 or more days before receiving the first dose (49%). The number of patients experiencing AEs were comparable between the two groups, 70% in the 5-day group vs 74% in the 10-day group. Serious AEs were seen 21% of patients in the 5-day group and 35% in the 10-day group.

Limitations:
The results from this study are limited by the lack of a placebo control group because the only available supply of matched placebo vials had been allocated to other ongoing randomized, controlled clinical trials. Given the limited health care resources during this time, the researchers planned to discharge patients as soon as possible, even if they did not finish their full course of therapy. As a result, only 44% of patients in the 10-day treatment group completed the full course of therapy. Patients who were not discharged were presumably those with more severe illness, which may account for the different rates of AEs seen in the two groups. Differences in baseline characteristics in regards to disease severity between the groups was a limitation that had to be accounted for when interpreting results. Lastly, another important limitation is that they did not have SARS-

CoV-2 viral-load results during or after treatment, owing to the variability in local access to testing and practices across the global sites.

Conclusion:
In this study, the patients had severe Covid-19 that did not require mechanical ventilation and were randomized to receive either a 5-day or 10-day course of remdesivir. The results did not show a significant difference between a 5-day course and a 10-day course of remdesivir. Future studies with a placebo control could potentially show the magnitude of benefit remdesivir can provide.

Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial [published correction appears in Lancet. 2020 May 30;395(10238):1694]. *Lancet*. 2020;395(10236):1569-1578.

Study Design: Multicenter, randomized, double blind, placebo-controlled trial

Description of Study:

Methods: Two-hundred-thirty-seven adult, non-pregnant patients who tested positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had oxygen saturation of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and were within 12 days of symptom onset were enrolled in the study. Patients were randomized (2:1) to receive either intravenous (IV) remdesivir (200 mg on day 1 followed by 100 mg on days 2-10 in single daily infusion) or placebo infusions for 10 days. Patients were assessed once daily by trained nurses using diary cards that captured data on a 6-category ordinal scale, (1 = discharged or having reached discharge criteria, 6 = death), and safety from day 0 to 28 or death. The safety assessment was done on days 1, 3, 7, and 10 and included daily monitoring for AEs. Vital signs were measured daily and 12-lead ECG on days 1 and 14.

Outcome Results: There was no statistically significant difference in the time to clinical improvement between the groups; median 21.0 days [IQR 13.0–28.0] in the remdesivir group *vs* 23.0 days [15.0–28.0] for placebo; HR 1·.3 [95% CI 0.87–1.75]. Although not statistically significant, in patients receiving remdesivir or placebo within 10 days of symptom onset, patients receiving remdesivir had a faster time to clinical improvement than those receiving placebo (median 18.0 days [IQR 12.0–28.0] *vs* 23.0 days [15.0–28.0]; HR 1·52 [0.95–2.43]. 28-day mortality was similar between the two groups (22 [14%] died in the remdesivir group *vs* 10 (13%) in the placebo group; difference 1·1% [95% CI −8.1 to 10.3]). In patients with use of remdesivir within 10 days after symptom onset, 28-day mortality was not significantly different between the groups, although numerically higher in the placebo group. Clinical improvement rates at days 14 and day 28 were also not significantly different between the groups, but numerically higher in the remdesivir group than the placebo group. No significant differences were observed

between the two groups in length of oxygen support, hospital length of stay, days from randomization to discharge, days from randomization to death and distribution of six-category scale at day 7, day 14, and day 28. AEs were reported in 66% of 155 patients in the remdesivir group and in 64% of patients in the control group.

Limitations: The power (58%) was insufficient to detect differences in clinical outcomes. Another limitation would be the initiation of treatment 12 days into symptoms of COVID-19 rather than at first sign of symptoms. Also, treatments other than remdesivir were permitted which could have affected the results.

Conclusion:
The data in the study showed that remdesivir was adequately tolerated but did not provide clinically significant antiviral effects in seriously ill patients with COVID- 19. Further studies with larger sample sizes, combination antivirals, or SARS-CoV-2 neutralizing antibodies need to be conducted in order to assess the efficacy in patients with severe COVID-19.

Contraindications[1,2,3,4]:

Hypersensitivity reaction: Contraindicated in patients with a history of clinically significant hypersensitivity reactions to VEKLURY or any components of the product.

Renal failure/dialysis: Study protocols contraindicate the use of remdesivir in patients with severe renal impairment (eGFR less than 30 mL/minute), renal failure, and in patients receiving dialysis or continuous renal replacement therapy.

Precautions[2,3,4]:

Pregnancy: Data regarding the use of remdesivir during pregnancy are insufficient to determine the drug-associated risk for major birth defects, miscarriages, or adverse maternal or fetal outcomes.

Lactation: There are no data regarding the presence of remdesivir in human milk, the effects on the breast-fed infant, or the effects on milk production.

Pediatric Use: Safety and efficacy of remdesivir have not been established in neonates, infants, or children younger than 12 years of age or weighing less than 40 kg.

Renal Impairment: Use not recommended in patients with an eGFR < 30mL/min

Hepatic Impairment: Transaminase elevations have been reported, including serious cases; monitoring recommended and discontinuation may be necessary.

Concomitant use: Not recommended in combination with chloroquine phosphate or hydroxychloroquine sulfate as it may result in reduced antiviral activity of remdesivir

Hypersensitivity including infusion-related and anaphylactic reactions: Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been reported during and following remdesivir administration. Signs/symptoms may include angioedema, bradycardia, diaphoresis, dyspnea, hypotension, hypertension, hypoxia, fever, nausea, rash, shivering, tachycardia, and wheezing; slowing infusion rate (maximum infusion time: 120 minutes) may be considered to potentially prevent these reactions.

Adverse Effects[1,2,3,4]:

Occurring >10% of patients:

- Hematologic: Anemia (15%)

Occurring >1% to <10% of patients:

- Endocrine & metabolic:
  - Hyperglycemia (1.8%)
  - Increased serum glucose (2.2%)
- Hepatic:
  - Acute hepatic failure
  - Increased serum alanine aminotransferase (1.5%)
  - Increased serum aspartate aminotransferase (2.8%)
- Renal:
  - Acute renal failure (2.8%)
  - Decreased eGFR (3.7%)
  - Increased serum creatinine (1.5%)
- Miscellaneous:
  - Fever (5%)
  - Nausea (5%)

Occurring in <1% of patients:

- Renal: Decreased creatinine clearance (0.6%)

Drug Interactions[1,2,3,4]:

Chloroquine, Hydroxychloroquine

- Concurrent use of CHLOROQUINE and REMDESIVIR may result in risk of reduced antiviral activity of remdesivir.

Dosing/Administration[12,3,4]:

Administration: As an IV infusion of 30 to 120 minutes for all patients

Adult Dosing

Hospitalized patients NOT requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO):

Initial: 200 mg IV once on day 1
Maintenance: 100 mg IV once daily for 4 days
May extend treatment for up to 5 additional days (10 days total) if patient does not demonstrate clinical improvement

Hospitalized patients requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO):

Initial: 200 mg IV once on day 1
Maintenance: 100 mg IV once daily for 9 days

Hospitalized children and adolescents 12 years and older weighing 40 kg or more NOT requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO):

Initial: 200 mg IV once on day 1
Maintenance: 100 mg IV once daily for 4 days
May extend treatment for up to 5 additional days (10 days total) if patient does not demonstrate clinical improvement

Elderly Dosing

Refer to adult dosing

Pediatric Dosing

Hospitalized children and adolescents 12 years and older weighing 40 kg or more NOT requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO):

Initial: 200 mg IV once on day 1
Maintenance: 100 mg IV once daily for 4 days
May extend treatment for up to 5 additional days (10 days total) if patient does not demonstrate clinical improvement

Hospitalized children and adolescents 12 years and older weighing 40 kg or more requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO):

Initial: 200 mg IV once on day 1
Maintenance: 100 mg IV once daily for 9 days

Hospitalized children younger than 12 years but weighing 40 kg or more NOT requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO):

Initial: 200 mg IV once on day 1
Maintenance: 100 mg IV once daily for 4 days
May extend treatment for up to 5 additional days (10 days total) if patient does not demonstrate clinical improvement

Hospitalized children younger than 12 years but weighing 40 kg or more requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO):

Initial: 200 mg IV once on day 1
Maintenance: 100 mg IV once daily for 9 days

Hospitalized infants, children, and adolescents weighing 3.5 to 39 kg NOT requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO):

Initial: 5 mg/kg/dose IV once on day 1
Maintenance: 2.5 mg/kg/dose IV once daily for 4 days is suggested by the FDA in the Emergency Use Authorization (EUA) statement
May extend treatment for up to 5 additional days (10 days total) if patient does not demonstrate clinical improvement

Hospitalized infants, children, and adolescents weighing 3.5 to 39 kg requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO):

Initial: 5 mg/kg/dose IV once on day 1
Maintenance: 2.5 mg/kg/dose IV once daily for 9 days is suggested by the FDA in the Emergency Use Authorization (EUA) statement
May extend treatment for up to 5 additional days (10 days total) if patient does not demonstrate clinical improvement.

Hospitalized neonates weighing 3.5 kg or more NOT requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO):

Initial: 5 mg/kg/dose IV once on day 1
Maintenance: 2.5 mg/kg/dose IV once daily for 4 days is suggested by the FDA in the Emergency Use Authorization (EUA) statement
May extend treatment for up to 5 additional days (10 days total) if patient does not demonstrate clinical improvement.

Hospitalized neonates weighing 3.5 kg or more requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO):

Initial: 5 mg/kg/dose IV once on day 1
Maintenance: 2.5 mg/kg/dose IV once daily for 9 days is suggested by the FDA in the Emergency Use Authorization (EUA) statement
May extend treatment for up to 5 additional days (10 days total) if patient does not demonstrate clinical improvement.

Renal impairment

Adult and Pediatric patients

eGFR 30 mL/minute or more: No dosage adjustment needed.
eGFR less than 30 mL/minute: Treatment is not recommended.

Hepatic impairment

Baseline hepatic impairment: There are no dosage adjustments provided in the manufacturers labeling (has not been studied).

Hepatoxicity during therapy:

ALT >10 times the ULN: Consider remdesivir discontinuation.

ALT elevation AND signs or symptoms of liver inflammation: Discontinue remdesivir.

Use in special circumstances[2,4]:

Pregnancy:

Data regarding the use of remdesivir during pregnancy are insufficient to determine the drug-associated risk for major birth defects, miscarriages, or adverse maternal or fetal outcomes.

Lactation:

It is not known if remdesivir is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.

Conclusion:

Remdesivir is an IV nucleoside antiviral that has been recently approved by the FDA for the treatment of COVID-19 in hospitalized adult and pediatric patients (aged $\geq$ 12 and weighing $\geq$ 40 kg). So far, it is the only FDA approved medication for COVID-19. Several clinical trials have been conducted to assess treatment of COVID-19 with remdesivir, but the data is conflicting. As trials continue to be done, much is still unknown about remdesivir including its use in pregnancy/lactation, neonates, infants, or children younger than 12 years of age or weighing less than 40 kg, and the overall potential for drug interactions. The safety endpoints of studies done have shown it to be well tolerated, with long-term effects still to be determined. Additionally, preliminary data from a study conducted by the WHO has not shown benefit when using remdesivir.

References:

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