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# Veklury® (remdesivir): Will mediocrity suffice in a pandemic?

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel β-coronavirus known to cause respiratory illnesses. It was first identified in December 2019 and was designated coronavirus disease 2019, or COVID-19.[1] As of November 29, 2020, the globally reported number of COVID-19 cases was over 61.8 million and the reported number of deaths was estimated to be 1.4 million.[2] In the United States (U.S.), as of December 1, 2020, there were a total of 13,447,627 cases and 267,302 deaths.[3] In more than 1.3 million laboratory-confirmed COVID-19 cases that were reported in the U.S. from January to May 2020, 14% of patients required hospitalization, 2% were admitted to the intensive care unit (ICU), and 5% died.[4] The National Center for Health Statistics (NCHS) uses ICD-10 codes from death certificates to produce provisional death counts associated with COVID-19.[5] Death count reporting with ICD-10 codes is an estimate since certifiers are asked to use their best medical judgement in determining cause of death. Certifiers may include statements such as 'presumed' cause of death (with or without confirmatory SARS-CoV-2 test) when there is reasonable degree of certainty.[5] On the other hand, certifiers may not associate COVID-19 with deaths from acute illnesses, even though SARS-CoV-2 can result in secondary infections (such as sepsis) which may lead to fatality.

The routes of human to human transmission include direct inhalation of contaminated sneeze or cough droplets as well as contact transmission through oral, nasal, and eye mucous. Indirect contact may occur through touching surfaces or objects contaminated by an infected person.[4] Once SARS-CoV-2 is in the host, it utilizes the human angiotensin converting enzyme II (ACE2) as an entry receptor.[6] The estimated incubation period for SARS-CoV-2 is 14 days from time of exposure, with a median incubation period of four to five days.[4] Infection can present in a wide variety of symptoms and the severity of the infection can range from asymptomatic to acute respiratory distress (ARDS) or death. In the US, 70% of infected individuals reported fever, cough, or shortness of breath, 36% had muscle aches, and 35% had headaches. Other symptoms included (but are not limited to) diarrhea, dizziness, rhinorrhea, anosmia, dysgeusia, sore throat, abdominal pain, anorexia, vomiting, pain in muscles or joints, coughing up blood, and kidney failure (as identified by protein or blood in urine).[4,6] Several studies reported viral infection to be accompanied by cardiac injury. In severe cases, infections have been reported to affect the central nervous system (CNS), resulting in seizures, stroke, and acute necrotizing hemorrhagic encephalopathy. Other possible disorders reported in hospitalized patients include abnormal blood clotting and venous thromboembolism.[6]

Clinical diagnosis of COVID-19 is based on clinical signs and symptoms, molecular diagnostics of viral genome by RT-PCR, chest X-ray or computed tomography scan, and serology blood tests.[4,6] The most common laboratory abnormalities are lymphopenia, leukopenia, thrombocytopenia, elevated CRP and inflammatory markers, elevated cardiac biomarkers, decreased albumin, elevated levels of D-dimer, elevated ferritin, elevated lactate dehydrogenase, and abnormal renal and liver function.[6] The Center for Disease Control (CDC) recommends obtaining nasopharynx samples for virologic molecular diagnostic and antigen testing.[4] Nasal swabs or oropharyngeal swabs are acceptable alternatives. Repeat testing may be required due to false negatives depending on the disease progression at the time of the test.[4,6]

Risk factors for developing severe infection include age ≥ 60 years, nursing home or long term care facility residence, and chronic medical conditions (of the data available, 32% had cardiovascular disease, 30% had diabetes, and 18% had chronic lung disease).[4] Other conditions that may lead to a high risk for severe COVID-19 include cancer, kidney disease, obesity, sickle cell disease, transplant recipients, and other immunocompromising conditions.4 Additionally, in a study from China, critically ill patients with COVID-19 and influenza co-infection were more prone to cardiac injury than those without influenza co-infection.[7]

On May 1, 2020, FDA granted Veklury® (remdesivir) an Emergency Use Authorization (EUA) to treat suspected or laboratory-confirmed COVID-19 in hospitalized adult and pediatric patients with severe infections.[8] On August 28, 2020, FDA revised the EUA to all hospitalized adult and pediatric patients, irrespective of their disease severity. On October 22, 2020, the FDA officially approved remdesivir use in hospitalized COVID-19 pos-

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itive adult and pediatric patients who were 12 years of age or older and who weighted at least 40 kg. Additionally, the EUA was revised to authorize use of remdesivir for treatment of suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients less than 12 years of age and weighing 3.5 kg to less than 40 kg.[8] It is important to note that EUA is different from FDA approval for treatment. An EUA of a drug is intended to enable access to federally secured stockpiles for experimental treatment purposes. Therefore, an EUA of a specific drug means that hospitals will need to request the medications through their states.[9]

## Criteria For Use

Per NIH guidelines, remdesivir is recommended in COVID-19 positive hospitalized patients requiring oxygen supplementation.[4] This includes patients who require oxygen delivery through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). In the setting of limited drug availability, remdesivir should be reserved for those who require supplemental oxygen as they have had the clearest benefit compared to those who require mechanical ventilation. It should not be used if patients are symptomatic for greater than ten days, given CDC findings showing a lack of replication-competent virus after ten days following symptoms onset.[4] Liver function tests and prothrombin time should be obtained in all patients before starting remdesivir.[8] Remdesivir may need to be discontinued if alanine transaminase (ALT) levels increase to greater than ten times the upper limit of normal and should be discontinued if there is an increase in ALT level along with signs or symptoms of liver inflammation. Remdesivir is not recommended for patients with eGFR <30 mL/min. Additionally, it is not recommended to administer remdesivir with chloroquine or hydroxychloroquine because they may decrease its antiviral activity.[4,10]

## Clinical Pharmacology

### *Mechanism of Action*

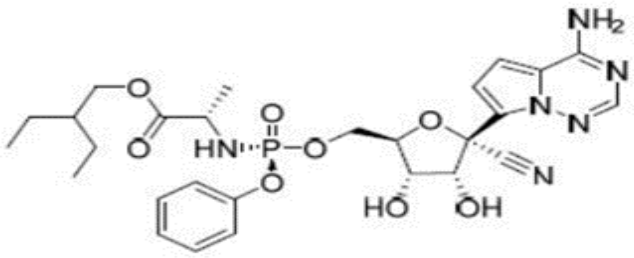
Remdesivir is a nucleotide prodrug of an adenosine analog, remdesivir-triphosphate (RDV-TP).[11] The metabolite RDV-TP competes with adenosine-triphosphate and incorporates into nascent viral RNA, inhibiting RNA-dependent RNA polymerases. It causes delayed viral RNA chain termination and inhibits viral replication, thereby limiting production of new viruses in the host.[11]

### *Pharmacokinetics*

Remdesivir is administered via intravenous infusion and is extensively metabolized by carboxylesterase 1 (CES1, 80%), with minor contributions from cathepsin A (10%) and CYP3A (10%).[10] Remdesivir is metabolized into nucleoside monophosphate intermediates GS-441524 and other non-active metabolites. Within cells, GS-441524 intermediate undergoes rapid conversion to pharmacologically active nucleoside triphosphate metabolite, GS-443902.[10] The percentage of protein binding in human plasma for remdesivir and GS-441524 are 88-93.6% and 2%, respectively.[9] The elimination half-lives for remdesivir and GS-441524 are 1 hour and 27 hours, respectively. The major route of elimination for remdesivir is through metabolism, with 10% of remdesivir being excreted in the urine. GS-441524 is primarily eliminated via glomerular filtration and active tubular secretion with a cumulative 49% and 0.5% eliminated in the urine and feces, respectively.[11]

**Table 1 | Select Remdesivir and Active Metabolites Pharmacokinetics[10,11]**

| | Remdesivir | GS-441524 |
|---|---|---|
| **Absorption** | | |
| $T_{max}$[a] (hours) | 0.97-0.68 | 1.51-2 |
| **Distribution** | | |
| Plasma Protein Binding | 88-93.6% | 2% |
| **Metabolism** | | |
| Primary | CES1 (80%) | Not significantly metabolized |
| Other | Capthesin A (10%)<br>CYP3A (10% | |
| **Elimination** | | |
| $T_{1/2}$[b] (hours) | 1 | 27 |
| Urine | 10% | 49% |
| Fecal | Not detected | 0.5% |
| **Chemical Structure** | | |




[a]Time to maximum plasma concentration; [b]Half-life

### *Pharmacodynamics*

Remdesivir is affected by CYP3A4, organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1 and OATP1B3), multidrug and toxin extrusion protein 1 (MATE1), and p-glycoprotein (P-gp).[11] In vitro, remdesivir is a substrate for CYP3A4, OATP1B1, and P-gp. In vitro, remdesivir is an inhibitor of CYP3A4, OAT1B1, OATP1B3, and MATE1.[11]

## Clinical Trials

The FDA approval for remdesivir was based off of data from three phase III clinical trials: ACTT-1, GS-US-540-5773, and GS-US-504-5774.[12] A list of ongoing trials involving remdesivir use for management of SARS-CoV-2 is included in **Table 2**.[13] Of note, this is not an exhaustive list and there are new trials constantly being piloted and added to clinicaltrials.gov. This review will include the three trials used for FDA approval of remdesivir in SARS-CoV-2 (summarized in **Table 3**) and an interim report published in October 2020 from the multinational phase III-IV SOLIDARITY trial conducted by the World Health Organization (WHO).

### *ACTT-1 (Sponsor: National Institute of Allergy and Infectious Disease [NIAID])[14]*

The ACTT-1 trial is a multi-national, randomized, double-blinded, placebo-controlled clinical trial of hospitalized adult subjects with mild/moderate or severe COVID-19 infections. Mild/moderate disease was defined as SpO2 >94% and respiratory rate

<24 breaths/min without supplemental oxygen. Severe disease was defined as participants meeting one or more of the following criteria: requiring invasive or non-invasive mechanical ventilation, requiring supplemental oxygen, an SpO2 ≤94% on room air, or tachypnea (respiratory rate ≥ 24 breaths/min). A total of 1,062 participants were randomized in a 1:1 ratio to receive either remdesivir (n=541) vs placebo (n=521). Remdesivir was administered as an intravenous infusion of 200 mg on day one, followed by 100 mg on days two to ten. The primary clinical endpoint was time to recovery within 29 days after randomization, as measured by an 8-point ordinal scale. Recovery was defined as moving from a poor clinical state (categories 4 to 8) to an improved clinical state (categories 1 to 3). The 8-point ordinal scale is outlined below:

1. Not hospitalized, no limitations on activities
2. Not hospitalized, limitation on activities and/or requiring home oxygen
3. Hospitalized, not requiring supplemental oxygen- no longer requiring ongoing medical care
4. Hospitalized, not requiring supplemental oxygen- requiring ongoing medical care (COVID-19 related or otherwise)
5. Hospitalized, requiring supplemental oxygen
6. Hospitalized, on non-invasive ventilation or high flow oxygen devices
7. Hospitalized, on invasive mechanical ventilation or ECMO
8. Death

The key secondary outcome was clinical status at day 15, as assessed on the ordinal scale. Other secondary outcomes of interest included time to discharge or National Early Warning Score (NEWS) of 2 or less (whichever occurred first) maintained for 24 hours and mortality at day 29.

Overall, patients in the remdesivir group had a shorter time to recovery than patients in the placebo group. The median time to recovery was 10 days in the remdesivir group vs 15 days in the placebo group (recovery rate ratio, 1.29 [95% confidence interval (CI) 1.12 to 1.49], p <0.001). For subjects with mild/moderate disease, the median time to recovery was five days in both the remdesivir and placebo groups (recovery rate ratio 1.22 [95% CI 0.82 to 1.81], not significant). Among subjects with severe disease, the median time to recovery was 11 days in the remdesivir group compared to 18 days in the placebo group (recovery rate ratio 1.31 [95% CI 1.12 to 1.52], significant). The rate ratio for recovery was largest among patients with a baseline ordinal score of 5 (rate ratio for recovery of 1.45 [95% CI 1.18 to 1.79], significant). Patients who underwent randomization during the first ten days after symptom onset had a recovery rate ratio of 1.37 [95% CI, 1.14 to 1.64, significant]. For patients who underwent randomization more than ten days after symptom onset had a recovery rate ratio of 1.20 [95% CI 0.94 to 1.52], not significant. The benefit of remdesivir appear to be more significant when given earlier. Overall, odds of improvement in the ordinal scale were higher in the remdesivir group at day 15 when compared to the placebo group (odds ratio 1.54 [95% CI 1.25 to 1.91], p <0.001, adjusted for disease severity). Patients who received remdesivir had a shorter time to discharge or to a NEWS of 2 or lower when compared to placebo (median of 8 days vs 12 days, hazard ratio 1.27 [95% CI 1.10 to 1.46], significant). The 29-day mortality was 11% for remdesivir group vs 15% for placebo group (hazard ratio 0.73 [95% CI 0.52 to 1.03], p=0.07, not significant).

### *GS-US-540-5773 (Sponsor: Gilead)*[15]

The GS-US-540-5773 trial was a phase III, multicentered, ran-

**Table 2 | Current Ongoing Trials with Veklury© (remdesivir) use in COVID-19**[13]

| |
|---|
| Remdesivir in COVID-19 Lahore General Hospital |
| Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734) in Participants from Birth to <18 Years of Age with Coronavirus Disease 2019 (COVID-19) |
| Antiviral Activity and Safety of Remdesivir in Bangladeshi Patients with Severe Coronavirus Disease (COVID-19) |
| Expanded access Remdesivir (RDV; GS-5734) |
| REMdesivir-HU Clinical Study and Severe Covid-19 Patients |
| Multicenter, Retrospective Study of the Effects of Remdesivir in the Treatment of Severe Covid-19 Infections |
| Remdesivir vs Chloroquine in Covid-19 |
| Study in Participants with Early Stage Coronavirus Disease 2019 (COVID-19) to Evaluate the Safety, Efficacy, and Pharmacokinetics of Remdesivir Administered by Inhalation |
| PK and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the US |
| A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared with Remdesivir Plus Placebo in Hospitalized Participants with Severe COVID-19 Pneumonia |
| Study to Evaluate the Efficacy and Safety of Remdesivir (GS-5734) Treatment of Coronavirus Disease 2019 (COVID-19) in an Outpatient Setting |
| Adaptive COVID-19 Treatment Trial 2 (ACTT-2) |
| Adaptive COVID-19 Treatment Trial 3 (ACTT-3) |
| ACTIV-5/Big Effect Trial (BET-A) for the Treatment of COVID-19 |
| ACTIV-5/Big Effect Trial (BET-B) for the Treatment of COVID-19 |
| Treatment for COVID-19: Canadian Arm of the SOLIDARITY Trial |
| An International Randomized Trial of Additional Treatments for COVID-19 in Hospitalized Patients Who Are All Receiving the Local Standard of Care- WHO-SOLIDARITY-GERMANY |
| The Efficacy of Different Anti-viral Drugs in COVID 19 Infected Patients |
| Inpatient Treatment with Anti-Coronavirus Immunoglobulin (ITAC) |
| Immune Modulators for Treating COVID-19 |
| Trial of Treatments for COVID-19 in Hospitalized Adults |
| I-SPY COVID-19 TRIAL: An Adaptive Platform Trial for Critically Ill Patients |
| ACTIV-3: Therapeutics for Inpatients With COVID-19 |
| **Compilation of trials obtained from clinicaltrials.gov on Nov 4, 2020** |

domized, open-label trial, which evaluated the safety and efficacy of five days versus ten days of remdesivir therapy in hospitalized patients with severe COVID-19. Severe COVID-19 was defined as radiographic evidence of pulmonary infiltrates and either an oxygen saturation of ≤94% on ambient air or patients who were receiving supplemental oxygen. Patients who were receiving mechanical ventilation and ECMO at screening were excluded. A total of 397 participants were randomized in a 1:1 ratio to receive either a five-day course (n=200) or ten-day course (n=197) of remdesivir therapy. Remdesivir was administered as a single daily intravenous infusion at a dose of 200 mg on day one, followed by 100 mg on days two to five or days two to ten. The primary endpoint was clinical status on day 14 assessed on a 7-point ordinal scale consisting of the following categories:

1. Death
2. Hospitalized, receiving invasive mechanical ventilation or ECMO
3. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices
4. Hospitalized, requiring low-flow supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related or not related to COVID-19)
6. Hospitalized, requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol for remdesivir administration); and
7. Not hospitalized.

The secondary endpoint included pre-specified exploratory endpoints such as time to recovery (as defined by improvement from a baseline score of 2 to 5 to a score of 6 or 7) and death from any cause.

Overall, subjects receiving a five-day course of remdesivir had similar clinical status at day 14 as those receiving a ten-day course (odds ratio for improvement 0.75 [95% CI 0.51 to 1.12], not significant). There were no statistically significant differences in recovery rates or mortality rates in the five-day and ten-day groups once adjusted for between-group differences at baseline. All-cause mortality at day 28 was 12% vs 14% in the five- and ten-day treatment groups, respectively.

### *GS-US-540-5774 (Sponsor: Gilead)*[16]

The GS-US-540-5774 trial was a phase III, multicentered, randomized, open-label trial which evaluated the safety and efficacy of five days versus ten days of remdesivir therapy as compared to standard of care in hospitalized patients with moderate COVID-19. Moderate COVID-19 pneumonia was defined as any radiographic evidence of pulmonary infiltrates and oxygen saturation >94% on room air. A total of 584 participants were randomized in a 1:1:1 ratio to receive standard of care (n=200), five-day course of remdesivir (n=191), or ten-day course of remdesivir (n=193). Remdesivir was administered as a single daily intravenous infusion at a dose of 200 mg on day one, followed by 100 mg on days two to five or days two to ten. The primary endpoint was clinical status on day 11 assessed on a 7-point ordinal scale. The 7-point ordinal scale included the same categories as those used in the GS-US-540-5773 study.

The secondary endpoint was the proportion of patients with adverse events throughout the duration of the study. Prespecified exploratory endpoints include change in clinical status on day 14, clinical improvement (as defined by an improvement of at least 2 points from baseline on the 7-point ordinal scale), and recovery (as defined by an improvement from a baseline score of 2 to 5 to a score of 6 or 7, or from a baseline score of 6 to a score of 7). Other exploratory endpoints were duration of hospitalization and all-cause mortality.

At day 11 post randomization, the odds of improvement in ordinal scale in the five-day remdesivir treatment group as compared to the standard of care group was statistically significantly higher (odds ratio of 1.65 [95% CI 1.09 to 2.48], p=0.02). The odds of improvement in clinical status at day 11 with the ten-day treatment group when compared to those receiving standard of care was not statistically significant (the proportional odds assumption was not met so no odds ratio was reported; p= 0.18 by Wilcoxon rank sum test). For the secondary endpoint, adverse events were experienced by 51% of patients in the five-day remdesivir group, 59% in the ten-day remdesivir group and 47% in the standard of care group. The difference in proportions of adverse events between the five-day treatment group and standard of care is 4.8% [95% CI -5.2% to 14.7%], p=0.36, not significant. The difference in proportions between the ten-day treatment group and standard of care is 12.0% [95% CI 1.6% to 21.8%], p=0.02, significant. Adverse events more common in the remdesivir groups include nausea, hypokalemia, and headache. For the secondary endpoint of clinical improvement at day 11, the difference in percentage between a five-day course of remdesivir and standard of care was 9.7% [95% CI 0.1% to 19.1%], significant. The difference in percentage between a ten-day course of remdesivir and standard of care was 4.8% [95% CI -5.0% to 14.4%], not significant. For recovery at day 11, the difference in percentage between five days of remdesivir and standard of care was 9.8% [95% CI 0.3% to 19%], significant. The difference in percentage between ten days of remdesivir and standard of care was 4.4% [95% CI -5.0% to 13.8%], not significant. A ten-day course of remdesivir trended toward clinical improvement and recovery when compared to the standard of care. However, the trends were not significant. The all-cause mortality at Day 28 was ≤2% in all treatment groups.

The lack of difference in odds of improvement for the ten-day remdesivir group may be due to its open-label design. In the ten-day remdesivir treatment group, although median length of treatment was six days the rates of discharge peaked on day 4 and then on day 11. In the five-day remdesivir treatment group, the rates of discharge peaked on day six. Due to the open-label nature of the study, the decision to delay discharge until day 11 may be in part influenced by the patient being in the ten-day treatment group. Adverse effects were significantly higher in the ten-day treatment group but were not significantly higher in the five-day treatment group. The possibility that additional hospitalization days and longer remdesivir treatment had a negative effect on outcome cannot be excluded. However, it is important to note that the rates of grade three or higher adverse events and serious adverse events were not higher in the ten-day treatment group when compared to the five-day treatment group or the standard of care group.

Interestingly, post hoc analysis on day 14 resulted in statistically significantly higher clinical status (as assessed by 7-point ordinal scale) in both the five-day remdesivir group (P=0.03) and the ten-day remdesivir group (P=0.03) when compared to the standard of care group. The increases in clinical statuses in the treatment groups were modest and were driven by the number of patients who were discharged.

**Table 3 | Summary of Results from ACTT-1, GS-US-540-5773, and GS-US-540-5774 Trials**

| Trial | Primary Outcome | Intervention | Population Subset | Results | P-value |
|---|---|---|---|---|---|
| ACTT-1 | Time to recovery (days)[a] | RDV[b] 200 mg on day one, followed by 100 mg on days two to ten<br>Placebo | Overall | RR[c] 1.29 (10 vs 15 days; 95% CI[d] 1.12 to 1.49) | < 0.001 |
| | | | Mild/Moderate | RR 1.22 (5 vs 5; 95% CI 0.82 to 1.81) | - |
| | | | Severe | RR 1.31 (11 vs 18, 95% CI 1.12 to 1.52) | - |
| GS-US-540-5773 | Clinical status[e] | RDV 200 mg day one, RDV 100 mg on days two to five<br>RDV 200 mg day one, RDV 100 mg days two to ten | Severe Disease | OR[f] 0.75 (95% CI 0.51 to 1.12) | - |
| GS-US-540-5774 | Clinical status[g] | RDV 200 mg day one, RDV 100 mg days two to five<br>RDV 200 mg day one, RDV 100 mg days two to ten<br>Standard of Care | Moderate | Improvement seen in 5-day RDV as compared to standard of care, OR 1.65 (95% CI 1.09 to 2.48) | 0.02 |
| | | | Moderate | No statistically significant improvement in 10-day RDV therapy as compared to standard of care | 0.18 |

[a]Recovery defined by 8-point ordinal scale within 29 days after randomization; [b]Remdesivir; [c]Recovery Ratio; [d]Confidence Interval; [e]Clinical status defined by 7-point ordinal scale on day 14; [f]Odds Ratio; [g]Clinical status defined by 7-point ordinal scale on day 11

### *SOLIDARITY TRIAL (Sponsor: WHO)*[17]

The SOLIDARITY trial is a phase III-IV, multicentered, open-label, randomized trial comparing different investigational interventions vs standard-of-care in hospitalized COVID-19 patients. In October 2020, an interim report was published from the SOLIDARITY trial. A total of 11,266 adults were randomized to either standard of care or four other COVID-19 interventional drugs in the interim report. One of the drugs studied was a ten-day course of remdesivir therapy (n=2,743) which was compared to standard of care (n=2,708). The primary endpoint was in-hospital mortality of remdesivir vs control, as estimated by log-rank death rate ratio (RR). RR was stratified for age and ventilation at entry. Secondary endpoints included ventilation and time to discharge. As of October 15, 2020, the SOLIDARITY trial did not find a statistically significant difference in mortality, initiation of ventilation, or duration of hospital stay between the remdesivir arm and the standard-of-care arm. Death rate ratios was RR=0.95 (95% CI 0.81 to 1.11, p= 0.50, not significant; numbers dead/randomized= 301/2743 remdesivir vs 303/2708 standard of care).

## Adverse Events and Drug Interactions

Common side effects from remdesivir include nausea, hypersensitivity, increased risk of transaminase elevation.[10] Remdesivir is contraindicated in those who have a history of clinically significant hypersensitivity reactions to remdesivir or any components of the product. Drug-drug interaction may occur with chloroquine phosphate or hydroxychloroquine sulfate. These drugs may decrease the antiviral activity of remdesivir when administered concomitantly.[10]

## Dosage and Administration

For dosage in adults and pediatric patients 12 years or older and weighing at least 40 kg, remdesivir is administered as an intravenous infusion with a dose of 200 mg on day one, followed by once daily maintenance doses of 100 mg starting from day two.[10] The recommended treatment duration for patients not requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is five days. Duration can be extended up to ten days if the patient is not clinically improving. For patients requiring invasive mechanical ventilation and/or ECMO, the recommended duration is ten days.[10] According to the COVID-19 NIH guideline, for hospitalized patients with COVID-19 who require invasive mechanical ventilation or ECMO, either dexamethasone or dexamethasone plus remdesivir are recommended. The rationale for remdesivir use is based on the ACTT-1 trial where a ten-day course of remdesivir was used on severe COVID-19 patients, including those on invasive mechanical ventilation or ECMO. However, it is important to note that ten days of remdesivir showed no observed difference in rate ratio for recovery when compared to the placebo group in patients on mechanical ventilation or ECMO at baseline (recovery rate ratio 0.98; 95% CI, 0.70 to 1.36).[14] Therefore, in times of medication shortage, remdesivir should be reserved for those who require supplemental oxygen but not severe enough to require invasive mechanical ventilation or ECMO.

## Special Populations

### *Pregnancy*

There are reports of decreases in corpora lutea, numbers of implantation sites, and viable embryos in female rats treated with remdesivir 14 days prior to mating and during conception.[10] There are insufficient data to evaluate drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.[10] Per NIH guideline, remdesivir should not be withheld from pregnant patients when there are no contraindications.[4] A study with 86 pregnant and postpartum hospitalized patients with severe COVID-19 infection received remdesivir for compassionate use. The therapy was well tolerated and had low rate of serious adverse

events.[4]

### *Pediatrics*

It is not known if remdesivir is safe and effective in children under 12 years of age or weighing less than 88 pounds (40 kg).[10] The Journal of the Pediatric Infectious Disease Society published an article summarizing guidance statements from a panel of pediatric infectious disease physicians and pharmacists from 18 geographically diverse North American institutions.[18] The guidance statements were endorsed by the Pediatric Infectious Disease Society. Key points from the article state that supportive care is enough for nearly all pediatric patients with COVID-19 due to higher incidence of mild illness in children (and available evidence indicating that pediatric outcomes are overall self-limiting and favorable). The decision to start antiviral for severely or critically ill children should be on a case-by-cases basis and clinicians should weigh individual risks and benefits. Factors such as chronic cardiac conditions, pulmonary conditions, obesity, and diabetes mellitus could be used to determine the risk vs benefit of antiviral therapy. For immunocompromised children, the suggestion is to reduce T-cell suppression in COVID-19 infected children. Potential for drug toxicity and drug-drug interactions should be considered for immunocompromised patients before initiation of antiviral therapy. If therapy is indicated in pediatric patients, remdesivir is preferred over hydroxychloroquine.[18]

## Cost and Availability

Gilead Sciences set the price for remdesivir in June 2020.[19] The price is different depending on if the patient has insurance or not. For patients with private insurance, remdesivir is $520 per vial. Since a course of five-day treatment would need 6 vials, the approximate cost for five days of treatment is $3,120 per patient. The price for those not covered by private insurance is $390 per vial.[19]

## Clinical Impacts

The FDA's approval of remdesivir use for COVID-19 was primarily based on the ACTT-1, GS-US-540-5773, and GS-US-540-5774 trials.[12] All three trials were powered to detect either time to recovery or clinical improvement of COVID-19 disease with remdesivir use.[14,15,16] In the ACTT-1 trial, both mild/moderate and severe infections were studied.[14] Although overall median time to recovery was shorter in the remdesivir group as compared to placebo, the difference in recovery time was most noticeable in the severe COVID-19 infection group. Severe COVID-19 infection in the study was defined as SpO2 ≤94% on room air, requiring oxygen supplementation (including ventilation or ECMO), or tachypnea (respiratory rate ≥ 24 breaths/min). In addition to median recovery time, the rate ratio for recovery was largest among patients with baseline ordinal score of 5. This group included patients who were receiving oxygen but not receiving high flow oxygen or noninvasive mechanical ventilation, suggesting more benefit of remdesivir use in patients who require oxygen but have a lower infection severity.[14] The GS-US-540-5773 trial was conducted only in severe COVID-19 infections, which they defined as patients with radiographic evidence of pulmonary infiltrates and either an oxygen saturation of ≤94% on ambient air or patients who were receiving supplemental oxygen (but excluding those who were receiving mechanical ventilation or ECMO).[15] This study population is similar to the severe disease population in the ACTT-1 trial. Results from GS-US-540-5773 suggest that the odds of improvement from a five-day course is not significantly different than that from a ten-day course of remdesivir therapy.[15] The GS-US-540-5774 trial was conducted on patients with moderate COVID-19 disease only, which is characterized by radiographic evidence of pulmonary infiltrates and oxygen saturation >94% on room air.[16] This study population is similar to the mild/moderate disease states in the ACTT-1 trial. The ACTT-1 trial showed no statistically significant difference in median recovery time between ten-day remdesivir treatment vs. placebo (the median time to recovery was five days in both the remdesivir and placebo groups).[14] Similarly, in the GS-US-540-5774 trial, the median length of treatment was six days in the ten-day remdesivir group.16 Discharge peaked at day four and day 11. The peak in day 11 discharge in the GS-US-540-5774 study may be due to the open-label nature of the trial. The decision to delay discharge until day 11 in the ten-day remdesivir group may have been subconsciously influenced by the fact that patients were in the ten-day treatment group. The delay in discharge and extended use of remdesivir may have led to increased incidence of low risk adverse events that led to an insignificant odds of improvement in ordinal scale at day 11 in the ten-day remdesivir group as compared to the standard of care group (p= 0.18). For a shorter five-day course of remdesivir treatment, results from the GS-US-540-5774 study showed a significantly higher day 11 odds of improvement in ordinal scale as compared to the standard of care (odds ratio, 1.65; [95% CI, 1.09 to 2.48], p=0.02).16 For COVID-19 infections of moderate severity where ten days of remdesivir is used, a 7-point or 8-point ordinal scale may be too broad to detect minor changes in clinical status, especially since benefits of remdesivir is coupled by increased incidence of low risk adverse events in a longer therapies. Furthermore, subgroup analysis of moderate COVID-19 patients who underwent randomization during the first ten days after symptom onset vs those who underwent randomization more than ten days after symptom onset may have been beneficial to look as well. However, that analysis was not conducted.

Although the ACTT-1, GS-US-540-5773, and GS-US-540-5774 trials all studied different illness severities, all three trials were similar in that they used SpO2 and oxygen requirement status of the patients to help define their infection severity.[14,15,16] The ACTT-1 trial showed shorter time to recovery with remdesivir treatment in severe COVID-19 infections after analyzing recovery times in both severe and mild/moderate illnesses. Additionally, they conducted subgroup analysis for patients in each baseline ordinal score in the 8-point ordinal scale.[14] Both the GS-US-540-5773 and GS-US-540-5774 trials were careful in recruiting patients with specific inclusion criteria to allow analysis on their predefined severe or moderate COVID-19 infections. However, the SOLIDARITY trial included COVID-19 infections of all severities and subgroup analysis was not stratified based on the different levels of infection severity. The death rate ratio was stratified for age and ventilation at entry.[17] However, for non-ventilated patients, death rate ratio was not stratified further based on disease severity, and subgroup analysis was not conducted on patients with moderate infections (that did not require oxygen supplementation) or severe infections (that did not require ventilation or ECMO). Furthermore, time from symptom onset to randomization was not included in the interim SOLIDARITY report. Benefits of remdesivir within ten days of symptom onset was shown in the ACTT-1 trial.[14] If remdesivir was started outside that timeframe for patients in the SOLIDARITY trial, the benefit of

remdesivir may have been lost.

The October 2020 interim report from the SOLIDARITY trial suggested that remdesivir was not effective for reducing mortality, reducing hospital length of stay, or preventing ventilator use.[17] Although SOLIDARITY reports no significant beneficial findings for remdesivir use in COVID-19, it is important to note their primary endpoint was to detect a significant difference in reduction of mortality.[17,20] The study may be insufficient to detect differences in their secondary endpoints, such as reduction of hospital length of stay, especially since factors such as infection severity and time from symptom onset were not considered. The differences in clinical improvements with remdesivir use in the ACTT-1 and GS-US-540-5774 trials were achieved when the studies were powered to detect a difference in clinical improvement, and when factors such as illness severity and time from symptom onset were considered. Due to the set-up of the SOLIDARITY trial, the only conclusive statement that can be made is that remdesivir does not have a mortality benefit as compared to standard of care.[14,16]

Results from the ACTT-1 trial indicate a shorter recovery time with remdesivir use and a shorter hospital length of stay. With the high cost of hospitalization, the cost of a five-day course of remdesivir may be justified if it means symptomatic improvement sufficient for discharge with decreased risk of disease spreading. Additionally, the cost of remdesivir may be justified if it can help free up hospital beds to help fight the pandemic.

## Conclusion

Remdesivir is currently the only antiviral drug approved for COVID-19. Studies report modest improvement in clinical status and time to recovery with remdesivir use. Although remdesivir resulted in modest improvement, due to the limited number of alternative options currently, it may still have a role in the management of COVID-19 infection until more effective options become available.

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# Personalized Medicine Corner

## TPMP and NUDT15 in Inflammatory Bowel Disease

**Benish Alam, PharmD**

### *Background*

Mercaptopurine (Purinethol®) and azathioprine (Imuran®), the prodrug of mercaptopurine, are two thiopurine agents used in inflammatory bowel disease (IBD). They are used for their immunosuppressive properties. Both of these thiopurines have active metabolites that incorporate themselves into the DNA to halt replication, and mercaptopurine also inhibits RNA synthesis by incorporating itself into strands, resulting in its immunosuppressive effects. These agents are valuable in caring for patients with Crohn's Disease in remission, or those requiring steroid-sparing regimens. They are also indicated for patients with ulcerative colitis in remission. Toxicities include severe myelosuppression, specifically leukopenia and thrombocytopenia.

### *TPMT and NUDT15*

Thiopurine methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15) enzymes are involved in the thiopurine metabolism pathway, and are responsible for creating inactive metabolites. Patients with decreased function of these enzymes are at high risk for side effects and toxicity, such as severe myelosuppression (leukopenia, thrombocytopenia) from the increase in toxic active metabolites. Patients with one fully functional allele, and one no function allele are considered to be intermediate metabolizers with decreased enzyme activity. Patients with two no function alleles are considered poor metabolizers with no enzyme activity. Intermediate or poor metabolizer status of TPMT is common in Caucasians (9%), while NUDT15 intermediate or poor metabolizer status occurs more frequently in Asian (17%) or Hispanic patients (8%). Patients may be tested for both of these enzymes, regardless of race or ethnicity.

### *Genotyping or phenotyping? That is the question.*

When assessing a patient for initiation on a thiopurine, the question arises of whether to genotype or phenotype. Per the Clinical Pharmacogenetics Implementation Consortium (CPIC), TPMT genotype and phenotype have high concordance, and clinical decisions can be made based upon either test. Clinical decisions for thiopurines can also be based upon genotype or phenotype of NUDT15, however standardization and validation of phenotype testing is still lacking for NUDT15. Phenotyping is not recommended in patients prescribed thiopurines for malignant diseases such as myeloid leukemias, or any disease state requiring blood transfusions. This is because the TPMT phenotype test is a measure of enzymatic activity in the red blood cells and a recent blood transfusion can render the test inaccurate. However, blood transfusions are less common with patients receiving thiopurines for IBD, and either phenotyping or genotyping can be assessed to guide dosing.

### *IBD guidelines stance on TPMT/NUDT15*

While the CPIC guidelines provide guidance on dosing adjustments once a test has been completed, the American Gastroenterology Association (AGA) guidelines conditionally recommend testing TPMT prior to initiating a thiopurine and retroactively if toxicity is expected due to TPMT deficiency. The British Society of Gastroenterology (BSG), National Institute for Health and Care Excellence (NICE), and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guidelines recommend testing TPMT prior to initiating therapy. To date, no guidelines recommend testing for NUDT15.

### *Dosing thiopurines based on TPMT and NUDT15 genotype testing*

The CPIC guidelines differentiate dosing recommendations based upon weight-based dosing, malignant and non-malignant indications, and also the effect of enzyme activity in drug levels reaching steady state. Because the normal starting doses for non-malignant conditions such as IBD are generally much lower than those used for malignant conditions, the guidelines emphasize that a patient may already be receiving an appropriately reduced dose. Clinically, we will often see no change in standard starting doses for IBD, as these patients are already on a reduced dose as compared to malignant indication doses. For most patients with a TPMT or NUDT15 enzyme deficiency, a 30-80% dose reduction is recommended for initial starting doses in IBD, and subsequent dosing is based on response and myelosuppression. The CPIC guidelines also provide guidance for dosing with patients that have a deficiency in either TPMT or NUDT15 but not the other enzyme.

### *Summary*

TPMT and NUDT15 testing can be used to guide initial dosing for azathioprine and mercaptopurine or retroactively if toxicity occurs and is suspected to be due to enzyme deficiency. Dosing can be guided by either genotyping or phenotyping testing in patients with IBD requiring thiopurines.

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