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Remdesivir: An Emergency Solution for the Treatment of Mild/Moderate and Severe COVID-19 Hospitalized Patients

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Abstract: ***Novel Coronavirus Disease (COVID-19) is caused by a zoonotic virus that belongs to the coronavirus family with a close relationship with the bat-SARS-like coronavirus strain BatCov RaTG13. Up until this day, no treatment option has been found to be completely effective against this virus clinically and theoretically. Veclury (remdesivir) is an RNA polymerase antiviral made by Gilead Sciences, Inc. and it has shown some promising results for patients hospitalized due to COVID-19 with mild/moderate and severe disease. According to this, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for healthcare providers permitting the emergency use of remdesivir for the treatment of COVID-19 hospitalized patients. The FDA based its EUA on data collected from clinical trials that used remdesivir. Examples of these trials are National Institute of Allergy and Infectious Diseases (NIAID) Adaptive COVID-19 Treatment Trial (ACTT-1) Trial in Subjects with Mild/Moderate and Severe Covid-19, Study GS-US-540-5773; Remdesivir for 5 or 10 Days in Patients with Severe Covid-19; a randomized, open label, multi-center clinical trial, and Study GS-US-540-5774; Effect of Remdesivir vs. Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19, A Randomized Clinical Trial. According to these trials, and others as well, remdesivir could be used as an intravenous infusion for 5 to 10 days depending on the severity of the disease.***

Keywords: COVID-19, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2, Remdesivir, Veclury

Introduction

As the latest pandemic of the Novel Coronavirus Disease, COVID-19; caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), sparked at the end of 2019, all smart minds and professional leaders have been working diligently to find a solution for the fight against this virus. The first case of the disease was identified in Wuhan Jinvintan Hospital as a patient who was admitted to the hospital suffering from pneumonia of unknown etiology [1]. Three bronchoalveolar lavage samples were collected from the patient which were then confirmed that the infection resulted from a virus that is closely related to the coronavirus family and belonged to the Betacoronavirus 2B lineage. Further testing showed that the virus and other available genomes of Betacoronavirus have a close relationship with the bat-SARS-like coronavirus strain BatCov RaTG13 thus the virus is a zoonotic virus and bats appear to be the carriers of it. The Novel coronavirus disease spread globally and it was declared a pandemic first by the World Health Organization, WHO, on March, 11 2020, which was then declared a national emergency in the United States of American on March, 13 2020 [2]. Signs and symptoms of the disease range from asymptomatic to severe pneumonia and death. Symptoms could appear 2-14 days after exposure to the virus which includes, but are not limited to, fever, dry cough, muscle or body aches, sputum production, shortness of breath, sore throat, headache, fatigue, new loss of taste or smell, and diarrhea [3]. Individuals at greater risk of developing severe illness and death are those over the age of 60 and those with underlying medical conditions such as cardiac and respiratory conditions. Globally, there have been 32,730,945 confirmed cases of COVID-19, including 991,224 deaths, reported to WHO [4], and about 7,059,087 cases in the US with a total of 204,033 deaths according to the CDC [5].

Remdesivir Development

Veklury (remdesivir, Gilead) is an investigational new drug manufactured by Gilead Sciences, INC., and its research started in 2009 for hepatitis C (HCV) and respiratory syncytial virus (RSV) [6]. In the beginning of May 2020, the Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for healthcare providers to use the antiviral medication Veklury (remdesivir) to treat suspected or confirmed patients with COVID-19 that are hospitalized with severe disease. The EUA extended the use of remdesivir for adults and pediatrics patients. Patients with low blood oxygen levels, requiring oxygen therapy, or needing more intensive breathing treatment such as mechanical ventilators were considered severe disease patients. On August 28, 2020, the FDA revised the EUA for the use of remdesivir to include all hospitalized adults and pediatrics patients with suspected or confirmed infection with COVID-19 regardless of the severity of the condition [7].

Mechanism of Action and Dosage

Remdesivir is a nucleoside ribonucleic acid (RNA) polymerase inhibitor which is considered a pro-drug that gets metabolized in the cells to an active nucleoside triphosphate metabolite [8]. The active metabolite acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA according to Gilead [9]. Remdesivir is given as an IV infusion only and the recommended dose depends on the severity of the disease. For adult patients, the recommended dosage is a loading of 200mg on day one followed by 100mg daily as maintenance. The duration of therapy depends on the patient's status and it ranges from 5 to 10 days where 5 days if the patient does not require mechanical ventilation and 10 days if the patient requires mechanical ventilation or

there was no improvement after the initial 5 days; therapy could extend to an additional 5 days. The IV infusion is administered over 30 to 120 minutes. For pediatric patients, the recommended dosage is the same as the one for adults unless the patient weighs 3.5kg to 40kg which then makes it a weight-based dosage. For patients weighing 3.5kg to 40kg, the recommended loading dose is 5mg/kg on day one followed by 2.5mg/kg starting on day two. The duration of therapy is the same as discussed above which ranges from 5 to 10 days depending on the need for invasive mechanical ventilation. Special consideration should be given for patients with renal disease as it is not recommended for patients with eGFR less than 30 mL/min, and it should be used with caution with patients who have underlying liver disease [9].

2. Clinical Trials

Many clinical trials have been carried out to figure out a solution for the fight against COVID-19. There are trials that have not been completed or started. Trials that have been addressing remdesivir as a treatment option for COVID-19 have been utilized in this review. Out of all literature out there, the following clinical studies have been chosen for this review.

Remdesivir in adults with severe COVID-19: a randomized, double-blind, placebo-controlled, multicenter trial [10]. This trial was conducted at ten hospitals in Hubei, China and it included adult patients (aged 18 and above) who were laboratory confirmed SARS-CoV-2 infection and severe disease. The primary objective for this study was "time to clinical improvement within 28 days after randomization" which basically means to improve patients' outcomes that ranged from death to discharge from the hospital. Secondary outcomes were focused on patients' outcomes at day 7, 14, and 28 after randomization, mortality at day 28 from any cause, use of invasive mechanical ventilation, oxygen therapy, hospital admission and stay, and patients developing nosocomial infection. The study was meant to enroll 325 patients with severe COVID-19 conditions but only 255 participants were screened, 18 excluded, and finally 237 were enrolled. There were 158 patients in the remdesivir group; 155 actually received treatment, vs. 79 patients in the placebo group; 78 continued the study (2:1 randomly assigned). Patients in the remdesivir group received intravenous remdesivir 200mg on day 1 followed by 100mg on days 2-10 infusions. Other medications were permitted to the patients in both groups which included lopinavir-ritonavir, interferons, and corticosteroids. Remdesivir therapy did not show significant difference compared to placebo for the primary outcome; 21 days vs 23 days, and also the time to clinical improvement results were similar; 21 days in the remdesivir group vs 23 days in the placebo group. Although the study did not show statistical significance, it is mentioned that patients who received remdesivir clinically improved faster than those who received placebo; 18 days vs. 23 days. Secondary outcomes were not significantly different between the two groups. Adverse events were not a big concern in this trial; however, 18 patients in the remdesivir group discontinued treatment due to adverse events vs 4 in the placebo group. In conclusion, this study did not show remarkable statistical or clinical significance of using remdesivir in treating adults with severe COVID-19 and professional judgment and further investigation are warranted to show the potential benefit of remdesivir as a successful agent against COVID-19.

Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: Clinical outcome and differences in post-treatment hospitalization status [11]. This study was conducted at Luigi Sacco Hospital, Milan, Italy and it included adult patients (18 years or above) males or non-pregnant females who had the infection which is confirmed by a positive reverse-transcriptase polymerase chain reaction (RT-PCR) and pneumonia confirmed by a chest X-ray or CT scan, and were mechanically ventilated or had an oxygen saturation (SaO2) level of <94 % in room air or a National Early Warning Score (NEWS)2 of ≥ 4; a system to standardize the assessment and response to acute illness. The primary outcome for this study was change in patients' hospitalization status on the 10th and 28th day of treatment. A 7-category ordinal scale was used to assess the primary outcome where 1 = no hospitalization with normal activities abilities, 2 = no hospitalization but with limitations of normal activities, 3 = hospitalization with no oxygen therapy need, 4 = hospitalization and needing oxygen treatment, 5 = hospitalization with oxygen treatment but no mechanical ventilation, 6 = ICU hospitalization and requiring mechanical ventilation and/or extra corporeal membrane oxygenation (ECMO), and 7 = death. The secondary outcome was premature treatment termination due to safety. Out of 50 patients that were to be on remdesivir, only 35 patients received at least one dose of remdesivir; 18 ICU patients and 17 Infectious Disease ward (IDW) patients. The dosing schedule was an intravenous loading dose of remdesivir 200mg on day 1 followed by 100mg days 2 to 10. Out of the 35 patients, 22 patients continued the treatment schedule and 13 patients discontinued treatment due to adverse events (n=8), death (n=4), or discharge (n=1). Overall, more IDW patients showed hospitalization status improvement after 28 days compared to ICU patients (88.2% IDW vs. 44.4% ICU). Only 1 patient in the IDW had no improvement and required high-flow therapy and/or non-invasive mechanical ventilation which might conclude that remdesivir was not as effective in critically ill patients. The study mentioned that it had some limitations which included the inability to have a controlled group, most of the patients treated with remdesivir had previously received lopinavir/ritonavir and hydroxychloroquine, and it could not predefine a virological follow-up.

National Institute of Allergy and Infectious Diseases (NIAID) Adaptive COVID-19 Treatment Trial (ACTT-1) Trial in Subjects with Mild/Moderate and Severe Covid-19 [12]. This was a randomized, double-blind, placebo-controlled study. Patients were enrolled in this study with laboratory positive SARs-COV-2 infection within the past 4 days and eligible patients were randomly assigned in a 1:1 ratio to receive with remdesivir or placebo (n=541 received remdesivir and n=521 received placebo plus standard of care). This was a global trial that included 60 sites in about

10 countries including the USA. Treatment with remdesivir was intravenous 200mg loading dose day 1 followed by 100mg once daily for days 2 to 10 (unless discharged earlier) in hospitalized patients who presented with lower respiratory tract infections. 1062 patients were enrolled out of which 105 (9.9%) patients with mild/moderate disease and 957 (90.1%) patients with severe disease; 285 patients (26.8%, n=131 on remdesivir) were on invasive mechanical ventilation/ECMO. Primary outcome for this trial was time to recovery from the time of enrollment and 28 days after on which patients achieved one of the first 3 categories; 1=no hospitalization no limitation on normal activities, 2=no hospitalization with some limitation and oxygen therapy, or 3=hospitalization due to infection control with no oxygen therapy or ongoing medical care. 10 days was the median time to recover in the remdesivir group vs 15 days in the placebo group (recover rate ration, 1.29; [95% CI 1.12 to 1.49]; p<0.001) which is statistically significant. The remdesivir group showed higher odds of improvement higher than the placebo group at day 15 (odds ratio, 1.6; [95% CI, 1.3 to 1.9]; p<0.001). 14-days Mortality has higher incidents in the placebo group; 11.9%, vs. the remdesivir group; 7.1%, after 607 recoveries (hazard ratio, 0.70 [95% CI 0.47, 1.04]; p=0.07). There were no major differences in the median time to recovery; 5 days, among patients with mild/moderate disease between both group (recovery rate ratio 1.22; [95% CI 0.82 to 1.81]); the odds of improvement in the ordinal scale between both groups on day 15 were: odds ratio, 1.46; [95% CI, 0.71 to 2.97]. Patients with severe disease at enrollment showed shorter median time to recovery in the remdesivir group; 11 days, compared to the placebo group; 18 days (recovery rate ratio, 1.31; [95% CI, 1.12 to 1.52]; p<0.001), and the odds of improvement in the ordinal scale between both groups on day 15 were: odds ratio, 1.56; [95% CI, 1.24 to 1.95]. Respiratory failure was reported as the most common serious adverse event reported in 5% of the remdesivir patients vs. 8% of the placebo patients. Other serious adverse events were reported in 21% of remdesivir patients and 27% of placebo patients. Non-serious adverse events were also reported in 29% of remdesivir patients and 33% of placebo patients. These non-serious adverse events included anemia, acute kidney injury, pyrexia, hyperglycemia, and increased transaminases. From these results we could conclude that the results were both statistically and clinically significant. Based on the primary endpoints, sample size, and adverse events, remdesivir shows superiority over placebo in the management of patients with mild/moderate and severe COVID-19.

Study GS-US-540-5773; Remdesivir for 5 or 10 Days in Patients with Severe Covid-19; a randomized, open label, multi-enter clinical trial [13]. This was a phase 3 trial that enrolled patients (12 years and above) that are hospitalized with confirmed SARS-COV-2 infection at 55 hospitals in about 8 countries including the USA. Patients with oxygen saturation less than or equal to 94% and/or radiological confirmed pneumonia were eligible for the trial. Patients were randomly assigned to either treatment with remdesivir for 10 days or remdesivir for 5 days (200 patients vs. 197 patients who received IV 200mg remdesivir on day 1 followed by 100mg once daily thereafter for 4 to 9 days plus standard of care) in a 1:1 ratio. The primary outcome was to assess clinical status on day 14 on a 7-point ordinal scale where 1=death, 2=hospitalized and receiving invasive mechanical ventilation or ECMO, 3=hospitalized and receiving non-invasive ventilation, 4=hospitalized and requiring low-flow oxygen devices, 5=hospitalized but only requiring medical care and not supplemental oxygen, 6=hospitalized but not requiring any treatment except for the continuation of the study, and 7=not hospitalized. Secondary outcome was to assess adverse events that would occur from the beginning of treatment up until 30 days after the last dose of treatment. Differences in baseline characteristics between both groups had to be adjusted which showed that both groups had similar clinical status at day 14 (odds ratio for improvement, 0.75; [95% CI 0.51 to 1.12]). Mortality rates were lower in the 5-day treatment group compared to the 10-day treatment group; 11.5% vs. 14.2%. Adverse events were similar between groups and the most common adverse events reported were nausea (10% in the 5-day group vs. 9% in the 10-day group), acute respiratory failure (6% vs. 11%), ALT increased (5% vs. 8%), and constipation (7% in both groups). Although it seems that the 5-day group had better outcomes than the 10-day group and that treatment duration would favor a shorter period of 5 days, the 10-day group had significantly higher patients with severe disease that required mechanical ventilation. In conclusion, the results of this date are not enough to make a clinical judgment in the course of treatment as the study meant to enroll patients with severe disease even though patients on mechanical ventilation were not eligible for the study. Also the two arms of the study were not equal in their baseline characteristics. Remdesivir could be used for the treatment of severe COVID-19 according to this study; however, the duration of therapy could range from 5 to 10 days depending on the improvement of each patient irrespectively to other patients.

Study GS-US-540-5774; Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19, A Randomized Clinical Trial [14]. This was a phase 3, open-label, multi-center, and randomized clinical trial that included hospitalized patients (12 years of age d and above) with moderate COVID-19 symptoms. Patients had confirmed SARS-COV-2 positive test with radiological confirmed pneumonia that did not require oxygen therapy. Moderate pneumonia COVID-19 was defined as pulmonary infiltrates and room-air oxygen saturation >94%. Patients were randomized in a 1:1:1 ratio to receive remdesivir for 10 days (n=193), remdesivir for 5 days (n=191), or standard of care or SOC (n=200). Remdesivir was given as a 200mg IV loading dose on day1 followed by 100mg IV maintenance dose thereafter. There were a total of 105 hospital sites in the United States, Europe, and Asia. The primary outcome was to assess clinical status on day 11 on a 7-point ordinal scale where 1=death, 2=hospitalized and receiving invasive mechanical ventilation or ECMO, 3=hospitalized and receiving non-invasive ventilation, 4=hospitalized and requiring low-flow oxygen devices, 5=hospitalized but only requiring medical care and not supplemental oxygen, 6=hospitalized but not requiring any treatment except for the continuation of the study, and 7=not hospitalized. Secondary outcome was to assess adverse events that would occur during the course of the study. Baseline characteristics including clinical status,

oxygen needs, and median symptoms duration were similar among all groups. Improvements in clinical status were higher in the 5-day treatment group compared to the SOC treatment group at day 11 of treatment (odds ratio, 1.65; [95% CI, 1.09 to 2.48]; p=0.017). This was not the case in the 10-day treatment group (odds ratio, 1.31; [95% CI 0.88 to 1.95]; p=0.183) which is not statistically significant. Mortality rate at day 28 was between 1-2% among all treatment groups. Adverse events were reported higher in the remdesivir groups compared to the SOC group. Most common adverse events reported among the 5-day, 10-day, and SOC groups as follows; nausea (10% vs. 9% vs. 3%), diarrhea (6% vs. 5% vs. 7%), hypokalemia (5%, vs. 7% vs. 2%), and headache (5% vs. 5% vs. 3%). Only 4 patients in the 5-day treatment group (2%) and 8 patients in the 10-day treatment group (4%) discontinued treatments due to adverse events. In conclusion, patients who received remdesivir showed statistical significant results compared to standard of care treated patients only in the 5-day treatment group which may suggest the shorter duration of treatment with remdesivir for patients with moderate COVID-19. However, longer duration of treatment might be warranted to overcome the disease while monitoring the patients for adverse events.

3. Discussion

COVID-19 pandemic has raised a tremendous concern not only for medical professionals and scientists but also to every person on the planet. It has been and still is a dilemma that must be addressed quickly. From the above studies that were mentioned, remdesivir could present a potential solution for this disease in terms of treating infected persons. Remdesivir might not be a standalone option for COVID-19 since the review only compared remdesivir alone with either placebo or standard of care treatment. The studies gave enough evidence for the FDA to issue an emergency use authorization granting the use of remdesivir in the treatment of COVID-19 for any patient admitted to the emergency room. Remdesivir should not be given to patients with renal insufficiency and should be given with caution to patients with hepatic disease. Treatment should be given as an IV loading dose of 200mg on day 1 followed by 100mg thereafter for a total of 5 to 10 days. More clinical trials are needed to confirm the use of remdesivir for the treatment of COVID-19 which is still a great threat for most people especially those with underlying cardiac, respiratory, or immunodeficiency diseases.

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