# Adverse Drug Event Reporting of Remdesivir

GAWALI VIJAY APPU[1], DIPAK A. JOSHI[2], SHYAMLILA B. BAVAGE[3], NANDKISHOR B. BAVAGE[4]

[1] *B. Pharmacy Final Year Student, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India*

[2] *Department of Pharmaceutics, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512 Maharashtra, India*

[3] *Department of Pharmacognosy, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512 Maharashtra, India*

[4] *Department of Pharmaceutical Chemistry, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512 Maharashtra, India*

***Abstract— Purpose; Remdesivir shows promise in the treatment of COVID19 patients. Despite this, it is still necessary to record potential drug side effects (PBL) for future decision-making. Same as the limited ADE data available before the COVID19 pandemic.***

## I. INTRODUCTION

Has proposed and studied several drugs for the treatment of COVID19 patients. However, there seems to be no cure so far, although dexamethasone. The most promising results are shown in well-designed studies. Remdesivir: a comparative study of 240 hospitalized patients. There is no significant improvement in the clinical benefits of COVID19 [8]. However, it was recognized this trial placebo, although this difference was not statistically significant. However, realized that this test was not strong enough.In a recent study, Beigel et al. (2020) found that in patients with severe COVID19 received remdesivir treatment for 10 days Related to faster recovery time, significant results were achieved in oxygenated patients. The mortality rate is 7.1% Remdesivir vs. 11.9% with placebo, although this difference was not statistically significant. In this study, most of the patients treated with Remdesivir discontinued treatment due to adverse events. This includes worsening cardiorespiratory status compared with patients receiving placebo. Adaptive Covid19-Research.Important in this case. Further data collection on the safety of repeated use of remdesivir for treatmentCOVID19 patients and the collection of additional data about them. The efficacy of patients with moderate to severe diseases. That's because of it reports of serious adverse effects with remdesivir including hepatotoxicity, with the ability of SARS-CoV-2 to induce alterations in hepatic function potentially a particular concern when prescribing remdesivir. This includes routine clinical care in addition to randomize.

## II. ARTICLE HIGHLIGHT

- Remdesivir is one of the recommended drugs for the treatment of COVID-19; however, security data is insufficient. Database for the past five years.
- Increased liver enzymes and kidney damage, increased creatinine in the blood, Heart failure, tachycardia or bradyarrhythmia, hypotension, and skin rash are the most common adverse events reported in the WHO database. Similar reports have been seen in the data of clinical trials.
- Majority of these ADEs were of a serious nature and many of the serious ADEs were fatal However, since there is no causal assessment, they cannot be assigned to Remdesivir with a confidence level of.
- Overall, the reported adverse events are consistent with the adverse drug reactions reported in clinical studies.

## III. PATIENTS AND METHOD

This principally involved interrogating the VigiBase®, which is the global pharmacovigilance A database maintained by the WHO, previously used to evaluate the side effects of hydroxychloroquine

[24,25].adverse events collected by national pharmacovigilance centers in more than 130 countries [26-28].Drugs are coded according to the expanded drug vocabulary of the World Health Organization, which includes: Classified by ATC (Anatomy and Therapeutic Chemistry) [29].According to the WHO Adverse Reaction Terminology and Medical Dictionary, the code of adverse event is .Regulatory Agency (MedDRA) [25.30].MedDRA vocabulary is organized by system Organs (SOC) are divided into preferred terms (PT) and low-level terms (LLT).people who had experienced one or more side effects took this suspicious drug.

## IV. DATA AND ANALYSIS

The study included the analysis of all suspected adverse reactions related to Redecive. Registered in VigiBase® within the past 5 years, i.e.January 1, 2015 to July 19, 2020Each report in VigiBase® is related to a person who may have one or more adverse events at the same time.AAM has been reclassified according to the medical dictionary Regulatory Agency (MedDRA); grouped at the System Organ Category (SOC) level And at the personal preference term (PT) level.The organs of the system, so, SOC, is a group of individual ADEs, coded in prefix terms, appearing in various forms. Favored Etiological name, p. ex.Infection and invasion, location of performance, page 3. Liver and biliary diseases, appointment, p. ex.Surgery and medical intervention, nutritional problems.

- Published and other studies on the side effects of Remdesivir

In addition to recording the AE observed with Remdesivir in VigiBase®, we also have ADE files in published research and Gilead presentations. The regulator compares and contrasts the results.We know that age and other factors affect the degree of side effects [36-38]. When these factors occur, this is worth paying attention to.They are not included in the design or analysis of the study.Also have new worries General drugs, because clinical trials usually include carefully selected patients Usually younger and less accompanied than patients receiving routine clinical care [39,40].

Consequently, we believe it is critical to analyze both spontaneous reports with remdesivir alongside data from the clinical trials to provide future guidance given current concerns appreciably more than number of persons. Overall, 1004 ADEs were reported from 439 people, giving an average 2.28 ADEs per person. Out of these 439 Individuals, 145 (33%) were from Europe, 288 (65%) from the region of Americas and 6 (1.3%) from the western pacific region. 267 (61%) were males and 163 (37.1%) were females, with gender not reported for 9 (2%) individuals. However, the majority of ADEs came from persons in the Americas (680–67.7%) Table 2 represents the characteristics of 1004 ADEs reported in the WHO database. All these are unique ADEs reported from 439 individuals. It was noted that around half of the ADEs were reported from the age group 18 to 64. More ADEs were reported from males than females (58.9%) and the majority of the ADEs were serious. Indications for the use of remdesivir for almost all cases was COVID – 19 infection (92.6%), with 5.8% ADEs fatal. Parameters to assess the causality, i.e., dechallenge action, dechallenge outcome, rechallenge action and rechallenge outcome was reported for a minority of the ADEs. However, as complete data was typically lacking assessment of causality was not possible.

## V. RESULTS

We will first summarize reported ADEs in the published studies as well as summaries provided by Gilead to the regulatory authorities before documenting the ADEs reported to VigiBase®. The ROR remained significant (3.52, 95% CI 1.70e7.28) when the analysis was retitrated to tocilizumab or glucocorticoid users in the reference group. Consistent results were observed in other sensitivity analyses and according age group. We identified 6574 reports with remdesivir or other drugs prescribed in COVID-19 patients. Among the 2603 reports with remdesivir, 302 were registered as cardiac effects. Among these cardiac reports, we found 94 bradycardia reports (31%), mainly from the United States (88, 93%). Patients with bradycardia had wide spectrum of age (61.2 ± 18.1 years, 6e90 minemax), were mostly men (53, 56%), with a mean body weight of 93 ± 28.3 kg. Mean treatment duration with remdesivir was 3.5 ± 1.8

days (range 1e9). Remdesivir was the sole suspected drug in 88 patients (94%).

## DISCUSSION

In this observational study including more than 6500 reports of COVID-19 patients, we found for the first time an association between remdesivir use and reports of bradycardia. Most of bradycardia reports with remdesivir were serious and some were fatal (17%). Our study suggests an increased risk of reporting bradycardia with remdesivir than other drugs. While such analysis could be subject to limitations as reporting bias, our results are in line with previous reports of cardiac events in remdesivir clinical trials [5]. This safety concern reminds us of two other cardiac safety signals with other RNA-dependent RNA-polymerase inhibitors. First, clinical development of the antiviral BMS986094 was discontinued after a phase II study due to serious cardiac events including heart rhythm disorders [8].

Second, in 2015, the FDA warned about serious bradycardia with hepatitis C treatments containing sofosbuvir [9]. The pharmacodynamic mechanism for bradycardia with remdesivir is still unknown. However, similarly to sofosbuvir, an effect on sinoatrial node function might be suggested.. Indeed, the active remdesivir metabolite is a nucleotide triphosphate derivative with similarity to ATP, known to slow sinoatrial node automaticity [10]. In the heart, ATP exerts negative chronotropic and dromotropic effects. The cardiac actions of ATP are mediated by adenosine its metabolite and by a vagal reflex triggered by ATP's stimulation of vagal sensory nerve terminals in the left ventricle [11].

Although this evidence is based on data from individual case safety reports, disproportionality analyses in pharmacovigilance databases remain important and provide reproducible information essential for early post-marketing surveillance [12,13]. These cardiac safety concerns should be particularly considered to limit the risk of cardiac adverse effects, particularly in the context of polypharmacy [14]. In addition, pharmacovigilance investigations are still necessary for cardiac risk with remdesivir, as a previous study reported the potential block of hERG (human ether-a-go-go gene) and prolongation of cardiac repolarization with remdesivir [15].

## CONCLUSION

These findings call for greater monitoring of liver enzymes during treatment, building on existing guidance, with the potential for dose adjustments, as well as monitoring renal function before and during treatment with remdesivir. Greater guidance can also be given by the authorities as more knowledge be existing comes available including potential doses of remdesivir in patients with COVID-19 with hepatic impairment or poor renal function.

## REFERENCES

[1] Jan H, Faisal S, Khan A, et al. COVID-19: review of epidemiology and potential treatments against 2019 novel coronavirus. Discoveries (Craiova, Rom). 2020;8

[2] Sanders JM, Monogue ML, Jodlowski TZ, et al. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. Jama. 2020. DOI:10.1001/jama.2020.6019

[3] Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. Crit Care. 2020;24(1):91.

[4] Scavone C, Brusco S, Bertini M, et al. Current pharmacological treatments for COVID-19: what's next? Br J Pharmacol. 2020; 177:4813–4824.

[5] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of covid-19 e final report. N Engl J Med 2020; 383:1813e26. https://doi.org/10.1056/NEJMoa2007764.

[6] Pelleg A, Belhassen B. The mechanism of the negative chronotropic and dromotropic actions of adenosine 5'-triphosphate in the heart: an update. J Cardiovasc Pharmacol 2010; 56:106e9. https://doi.org/10.1097/FJC.0b013e3181e0f8b2.

[7] Coloma PM, Trifiro G, Patadia V, Sturkenboom M. Post marketing safety sur- veillance: where does signal detection using electronic healthcare records fit into the big picture? Drug Saf 2013; 36:183e97. https://doi.org/10.1007/ s40264-013-0018-x