ejpmr, 2022,9(1), 367-371

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

STUDY OF CLINICAL MANIFESTATIONS AND OUTCOME OF RTPCR NEGATIVECOVID PNEUMONIA PATIENTS RECEIVING INJECTION REMDESIVIR.

Atharva Ajay Kulkarni*, Meenakshi Ashesh Bhattacharya, Sandesh Malu, Shrutika Kamble and Omkar Oak

Department of Medicine, Government Medical College and Hospital, Near Panchakki road,Aurangabad 431001.

***Corresponding Author: Dr. Atharva Ajay Kulkarni**

Department of Medicine, Government Medical College and Hospital, Near Panchakki road,Aurangabad 431001.

Article Received on 03/11/2021 **Article Revised on 24/11/2021** **Article Accepted on 15/12/2021**

ABSTRACT

Background: RTPCR is considered gold standard for diagnosis but because of False Negatives, HRCT scans are usedas an aid for radiological diagnosis of COVID-19. Remdesivir is an antiviral pro-drug used to treat COVID-19 positive cases. But there are no treatment options for patients presenting as COVID pneumonia but testing negative by RTPCR. **Methods add Period:** We conducted a cross sectional observational study to find the outcome of RTPCR Negative Pneumonia patients receiving Remdesivir. Between June 2020 to January 2021, patients who tested negative after an RTPCR swab for SARS-CoV2 but were clinically or radiologically suspected to have COVID-19 were administered Remdesivir (200 mg on day one followed by 100 mg for the next four days) and their outcome, with demographic, clinical and radiologic characteristics of COVID-19 were assessed. **Results:** Out of 158 RTPCR Negative Pneumonia patients who received Remdesivir, 150 recovered (94.9%) and were discharged. 95 patients (60.12%) were Males. 61 patients belonged to age groups between 40-59 years (38.6%) and 65 patients were of the age ≥60 years (41.1%). 54 patients (34.1%) had some comorbidity, Hypertension being the most common, in 37 patients (23.4%). 91 patients (57.5%) belonged to Stage IIB. 39 patients (24.6%) had oxygen saturation <80% at admission of which 35 were discharged giving a recovery rate of 89.7%. **Conclusion:** It was observed that 94.9% RTPCR Negative COVID-19 pneumonia who received Inj. Remdesivir recovered and were discharged.

KEYWORDS: COVID-19, RTPCR, Negative, Pneumonia, Remdesivir.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-COV-2). The first case was identified in Wuhan, China, in December 2019 and reported to WHO (World Health Organization) on 31 December 2019. Later, it has spread worldwide leading to the ongoing pandemic. On January 30, 2020, the WHO declared the COVID-19 a global health emergency and on 11 March 2020 the WHO declared COVID-19 as a global pandemic.

In India, the first case of COVID-19 was reported in Kerala on January 27,2020 and in Maharashtra it was reported on 9 March 2020 while in Aurangabad it was reported on 15th March 2020.

SARS-COV-2 is member of family Coronaviridae and of the order Nidovirales and suborder Coronavirinae. It is enveloped and positive sense single stranded RNA Virus.[1] It spreads directly fromperson to person through respiratory route via aerosols or formation of droplet nuclei and indirectly contact via fomites and contaminated surfaces.[2],[3]

Clinical features of COVID-19 are variable and range from asymptomatic or mild disease to severe illness and mortality. They depend upon the clinical stage and mostly include fever, malaise, sore throat,cough, nausea, loss of taste and smell, body ache, and can progress to breathlessness with lower respiratory tract infection and respiratory failure with septicemia and multiorgan dysfunction.[4]

The gold standard test for virus detection is microbiological RT PCR technique by testing a nasopharyngeal swab, however the sensitivity of the results in clinical practice may depend on the period of symptoms, viral load and quality of the test sample.[5] A vital issue with RTPCR is the risk of eliciting false negative as well as false positive results[6]. In view of the same, High Resolution Computerized Tomography of the chest in suspected patients is being used to find out the severity of the disease. CORADS (COVID-19 Reporting And Data System) is used to identify the extent of pulmonary involvement in COVID19 and is helpful in predicting the diagnosis in COVID-19 patients with moderate to severe symptoms albeit with low specificity.[7]

Till date, there is no definitive treatment for COVID -19.

Potential pharmacological treatments include antiviral drugs and novel therapeutic agents.[8] Remdesivir is an antiviral prodrug used to treat COVID- 19 in many health care facilities and is also recommended in Indian Trial Data by DGCI (Drug Controller General of India) and found to be shorten the time to recovery in patients who are hospitalized for COVID-19.[9], [10] However there are no advisories regarding treatment of patients who present clinically with findings suggestive of COVID19 but test negative for SARS CoV2 via RTPCR. Hence, we performed a systematic review to find the efficacy of Remdesivir in patients with clinical and radiological picture suggestive of COVID Pneumonia but with RTPCR Negative for SARS CoV2.

MATERIALS AND METHODS

Approval of the institutional ethics committee was taken prior to commencement of the study. Since Remdesivir was approved for treatment of RTPCR Negative patients only after 23rd September 2020[11], all patients who received it before this period were informed about potential benefits and adverse effects and written and informed consent regarding same was obtained.

Primary objective of the study is to find Outcome of RTPCR Negative COVID Pneumonia patients Receiving Injection Remdesivir.

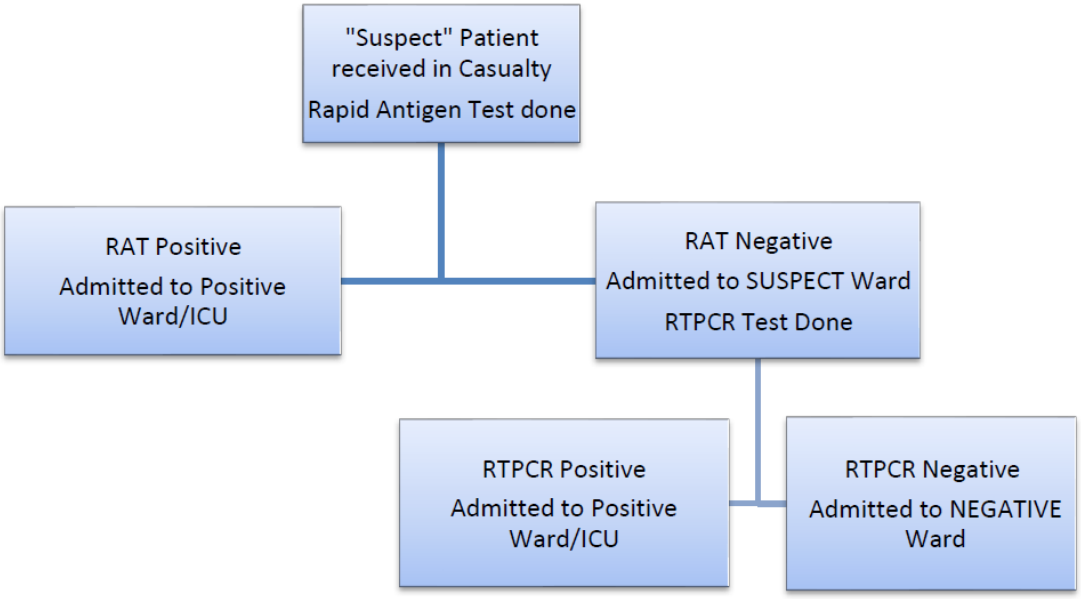
Secondary Objectives

1) To study their Demographical characteristic
2) To study their Comorbidities
3) To Study Stages of COVID-19
4) To study the Radiological Presentation of Study Populations

This was a cross sectional observational study conducted in the Department of Medicine, Government Medical College and Hospital, Aurangabad between the study period of June 2020 to January 2021.

Inclusion Criteria: All patients who were admitted as having clinical Pneumonia with or without radiographic evidence and had RTPCR test negative were included in the study.

Exclusion Criteria: All patients of Pneumonia detected to be RTPCR Positive for COVID-19 were excluded from the study. All patients who had Pneumonia secondary to an identifiable cause were alsoexcluded.



All the patients presenting with signs and symptoms suggestive of COVID-19 including fever, cough, breathlessness were subjected to a Rapid Antigen Test (RAT) in the Casualty of the hospital. Those who tested Positive were shifted immediately to a designated COVID-19 Positive Ward or Intensive Care Unit based on patient's clinical status. Those who tested Negative were admitted in a separate ward designated for COVID-19 Suspects from where they were tested for COVID-19 as per ICMR guidelines. An RTPCR swab for SARS CoV2 was taken and sent to Viral Research and Diagnostic Laboratory, Department of Microbiology, Government Medical College and Hospital, Aurangabad in appropriate viral transport media (VTM) and tested for RTPCR Biorad cfx96. All patients who were detected as Positive were excluded and those detected to be Negative were shifted to a separate ward where their clinical history, examination, laboratory investigations and radiographic investigations were reviewed. All eligible patients were started on Injection Remdesivir, as per treatment guidelines issued by Directorate of Medical Education and Research, after ruling out any contraindications including deranged Liver and Kidney function tests due to any cause and taking a written informed consent from relatives and explaining them the nature and progression of illness and course of treatment

and potential adverse effects. Patients were started on Injection Remdesivir with dose of 200 mg on day one infused over one hour followed by 100 mg for the next four days and were monitored clinically for recovery or deterioration in form of requirement of oxygen and reduction of signs and symptoms. Outcome was noted in form of discharge or death of the patient.

OBSERVATIONS AND RESULTS

Table 1: Distribution of patients based on gender.

Males	95
Females	63

Table 2: Distribution of patients based on age and their outcome.

< 40	32	Discharge	32	Death	0
40-59	61	Discharge	59	Death	2
≥ 60	65	Discharge	59	Death	6

Table 3: Prevalence of pre-existing comorbidities in patients.

Hypertension	37
Diabetes mellitus	31
More than one comorbidity	19

Table 4: Distribution of patients in clinical categories.

Stage I	24
Stage IIA	43
Stage IIB	91

(Stage I: Asymptomatic/Mild symptoms; RR<24/m & SpO2 > 94% RA
Stage IIA: Symptomatic with Mild to moderate pneumonia with no signs of severe disease; RR: 24-30/m OR SpO2: 90-94% RA
Stage IIB: Symptomatic patient with Severe Pneumonia; RR>30/m OR SpO2 < 90% OR <94% withOxygen, ARDS, Septic Shock)

Table 5: Baseline oxygen saturation levels of patients on admission and their outcome.

>94%	25	Discharge	24	Death	1
80-94%	94	Discharge	91	Death	3
<80%	39	Discharge	35	Death	4

Table 6: CT severity scores calculated using high resolution computerized tomography and subsequent outcome of patients

<13	76	Discharge	73	Death	3
≥13	34	Discharge	32	Death	2

(CT scans done in a total of 110 patients out of 158)

Table 7: Duration (in days) in which patient was started on injection Remdesivir.

≤3 days	122	Discharge	115	Death	7
>3 days	34	Discharge	33	Death	1
>7 days	2	Discharge	2	Death	0

Table 8: Outcome of admitted patients.

Patients	Discharge	Death
158	150	8

DISCUSSION

A total of 158 patients of Pneumonia who tested RTPCR negative for SARS CoV2 and had no contraindications from June 2020 to January 2021, were treated with Injection Remdesivir as per Maharashtra task force SOPs. Out of a total of 158, 95 patients (60.12%) were Males while 63 patients (39.87%) were Females (Table 1). The age distribution of the patients was varied (Table 2) wherein 32 patients were of age less than 40 (20.2%) all of whom were discharged. 61 patients belonged to age groups between 40 to 59 years (38.6%) of which 59 were subsequently discharged and 2 patients died; and 65 patients were of the age 60 years and above (41.1%) of which 59 patients were discharged and 6 patients succumbed to death. 54 of our patients (34.1%) had some comorbidity (Table 3) of which Hypertension was the most common, seen in 37 patients (23.4%) followed by Diabetes Mellitus in 31 patients (19.6%). 19 patients (12.01%) had more than one comorbidity. On basis of clinical presentation patients were divided into three groups[11] (Table 4). 24 patients (15.1%) belonged to Stage I that is patients having asymptomatic disease or those having mild symptoms and Respiratory Rate less than 24per minute and oxygen saturation more than 94% on room air. 43 patients (27.2%) belonged to Stage IIA which included symptomatic patients with mild to moderate pneumonia with no signs of severe disease and having a respiratory rate between 24 to 30 per minute or oxygen saturation between 90 and 94% on room air. A large majority of 91 patients (57.5%) belonged to Stage IIB which included symptomatic patient with Severe Pneumonia that is having a respiratory rate more than 30 per minute OR oxygen saturation less than 90% on room air OR having oxygen saturation less than 94% with requirement of supplemental oxygen or those in acute respiratory distress syndrome or Septic Shock.

Baseline oxygen saturations of patients were noted and their subsequent course was monitored (Table 5). It was noted that at admission, 25 patients (15.8%) had oxygen saturation level of more than 94% at room air of which 24 patients were discharged giving a recovery rate of 96%. 94 patients (59.4%) had oxygen saturation between 80 to 94% of which 91 patients were discharged giving a recovery rate of 96.8%. 39 patients (24.6%) had oxygen saturation level less than 80% at admission of which 35 patients recovered and were subsequently discharged giving a recovery rate of 89.7%. In the 110 patients in whom High Resolution Computerized Tomography had been performed prior to, or at beginning of admission, an arbitrary value of CT Severity Score 13 was chosen to divide patients as it indicated involvement of half of the 25 divided lung zones. It was found that (Table 6) 76 patients (69.09%) had a CT Severity Score of less than 13, of which 73 patients recovered and were discharged; while 34 patients (30.9%) had a CT Severity Score of

more than 13, of which 32 patients recovered and were discharged. The time of administration of Remdesivir and its correlation with clinical outcome was sought (Table 8). It was found that 122 (77.2%) patients received the first dose within 3 days of symptoms onset of which 115 patients recovered and were discharged. 34 patients received their first dose within 3 to 7 days of symptom onset (21.5%) of which 33 patients were subsequently discharged post recovery. At the end of the study, we found out that 150 patients (94.9%) recovered and were eventually discharged, and 8 patients (5.1%) succumbed to death.

The primary outcome of the study was sought in form of clinical recovery of the patient in form of decrease in requirement of supplementary oxygen, maintaining oxygen saturation levels on ambient room air after a six-minute walk test and improvement in clinical signs and symptoms.

In spite of extensive research for studies done for a similar group of patients, we could not find any studies which could guide us regarding the choices for treatment for such patients. Hence it was planned to treat these patients who presented with clinical and radiological features similar to COVID-19 but with an RTPCR swab negative for SARS CoV2, similarly to those who tested positive for it.

At the end of the study, we found out that majority of the patients who presented clinically and/or radiographically with features suggestive of Pneumonia and tested negative for SARS CoV2 by RTPCR testing recovered after a 5-day dosing of Injection Remdesivir.

Limitations of the study

The results obtained in this study couldn't be compared with any other studies because in spite of extensive research, we failed to find out any other studies which focused on treatment of RTPCR negative patients who presented with manifestations of COVID-19.

Another limitation deduced from a study done at the institutional level showed that of the total 15207 cases admitted as COVID Suspects from March 2020 to June 2021, 10158 were detected as RTPCR Positive for SARS CoV2 while 5049 ended up reporting Negative. Most of them were excluded from our study as they had other underlying diseases contributing to pneumonitis as a secondary manifestation of their primary illness or had clinical primary pneumonitis but had contraindications to use of Remdesivir resulting in them not being able to be included as a part of this study.

Also, we tried to present our observations about efficacy of injection Remdesivir in RTPCR Negative patients only. However, to ideally determine efficacy, a control group would have been appropriate. As this was an observational study, it carries all the limitations of an observational, cross -sectional study. Due to huge workload and lack of adequate manpower, a detailed data collection could not be possible. Treatment guidelines should be individualized as much as possible and started based on all three – RTPCR report, clinical presentation and radiological features and not simply relying on the RTPCR report for SARS CoV2. However, it needs to be pointed out that Remdesivir as an antiviral alone isn't sufficient as a treatment module, because 8 patients succumbed to death despite receiving the full dose as per protocol as it is seen in RTPCR positive patients also. Hence further research needs to be taken upregarding use of other medications including newly approved drugs for confirmed cases of SARS CoV2 positive in the negative counterparts with similar presentations as well. With time, as the alarming burden of COVID-19 positive patients increases, a corresponding silent and hidden load of COVID-19 Negative patients will cause its toll on the healthcare setting and better diagnostic as well treatment options must be researched for and developed so as to supply adequate care for these patients.

CONCLUSION

In the present study RTPCR Negative COVID-19 like pneumonia patients were treated with Inj. Remdesivir. Most of these patients were symptomatic and had oxygen saturation levels less than 94% at baseline and required oxygen support. Majority of patients received Remdesivir within 3 days of symptom onset. It was observed that 94.9% RTPCR Negative COVID-19 pneumonia who received Inj. Remdesivir recovered and were discharged.

REFERENCES

1. V'kovski, P., Kratzel, A., Steiner, S. et al. Coronavirus biology and replication: implications for SARS-CoV-2. Nat Rev Microbiol, 2021; 19: 155–170. https://doi.org/10.1038/s41579-020-00468-6.
2. Organisation WH. Modes of transmission of virus causing COVID-19: implications for IPC precaution recommendations. 2020. https://www.who.int/news-room/commentaries/detail/modes-of- transmission-of-virus-causing-covid-19-implications-for-ipc-precaution-recommendations.
3. Karia R, Gupta I, Khandait H, Yadav A, Yadav A. COVID-19 and its Modes of Transmission [published online ahead of print, 2020 Sep 1]. SN Compr Clin Med. 2020;1-4. doi:10.1007/s42399-020-00498-4.
4. Cascella M, Rajnik M, Aleem A, et al. Features, Evaluation, and Treatment of Coronavirus (COVID-19) [Updated 2021 Apr 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan
5. Goudouris ES. Laboratory diagnosis of COVID-19. J Pediatr (Rio J), 2021; 97(1): 7-12. doi:10.1016/j.jped.2020.08.001
6. Tahamtan A, Ardebili A. Real-time RT-PCR in COVID-19 detection: issues affecting the results. Expert Rev Mol Diagn, 2020; 20(5): 453-454.

doi:10.1080/14737159.2020.1757437.
7. Xu B, Xing Y, Peng J, et al. Chest CT for detecting COVID-19: a systematic review and meta- analysis of diagnostic accuracy. Eur Radiol, 2020; 30(10): 5720-5727. doi:10.1007/s00330-020-06934-2 8: James M. Sanders, PhD, PharmD. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19).
8. A Review. JAMA, 2020; 323(18): 1824-1836. doi:10.1001/jama.2020.6019.
9. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, et al. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med, 2020.
10. Young, Barnaby et al. The place for remdesivir in COVID-19 treatment The Lancet Infectious Diseases, 21(1): 20–21.
11. Recommendations for the Management of COVID-19 patients, Maharashtra COVID Task Force, dated 07/04/2021.
12. DMER, Mumbai Letter 615/2020 dated 15/09/2020 with attached Advisory for Remdesivir- Emergency Use Approval.
13. Eastman R.T., Roth J.S., Brimacombe K.R., Simeonov A., Shen M., Patnaik S., Hall M.D. Remdesivir: a review of its discovery and development leading to emergency use authorization fortreatment of COVID-19. ACS Cent. Sci, 2020; 6: 672–683. doi: 10.1021/acscentsci.0c00489.
14. Brown A. J.; et al. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. Antiviral Res, 2019; 169: 104541.10.1016/j.antiviral.2019.104541.
15. Wang M.; et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res, 2020; 30: 269–271. 10.1038/s41422-020-0282-0.
16. Sheahan T. P.; Sims A. C.; Leist S. R.; Schafer A.; Won J.; Brown A. J.; Montgomery S. A.; Hogg A.; Babusis D.; Clarke M. O.; Spahn J. E.; Bauer L.; Sellers S.; Porter D.; Feng J. Y.; Cihlar T.; JordanR.; Denison M. R.; Baric R. S. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat. Commun, 2020; 11(1): 222.10.1038/s41467-019-13940-6.
17. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet, 2020; 395: 1569-1578.
18. Yang Y, Yang M, Shen C, et al. Laboratory diagnosis and monitoring the viral shedding of 2019- nCoV infections. medRxiv preprint. DOI:10.1101/2020.02.11.20021493.
19. Mallett, S., Allen, A.J., Graziadio, S. et al. At what times during infection is SARS-CoV-2 detectable and no longer detectable using RT-PCR-based tests? A systematic review of individual participant data. BMC Med, 2020; 18: 346. https://doi.org/10.1186/s12916-020-01810-8.