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# EFFICACY OF REMDESIVIR VERSUS REMDESIVIR PLUS TOCILIZUMAB IN MODERATE TO SEVERE COVID-19 PATIENTS ADMITTED IN THE CRITICAL CARE UNIT OF A TERTIARY CARE HOSPITAL IN WEST BENGAL, INDIA

Anaesthesiology

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## ABSTRACT

**Background And Aims:** Severe corona virus infection is often associated with hyper immune response and liberation of inflammatory cytokines. Anti-interleukin-6 receptor monoclonal antibody like tocilizumab might be effective in corona virus infection. Present study was designed to assess the effect of adding tocilizumab to remdesivir and other supportive therapy in management of critically ill covid-19 patients.

**Methods:** This Randomized open-level clinical trial was done in 50 critically ill Covid-19 patients (from December 2020 to February 2021). They were randomly allocated in two group; to receive either injection remdesivir (Group R) or injection remdesivir plus tocilizumab (Group RT) intravenously. Patients were assessed using daily record sheets capturing data on the six-category ordinal scale and safety profile from day-1 to day-28 or discharge or death. Other clinical data were recorded using the WHO International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) case record form.

Primary endpoint with respect to the efficacy of the drugs was based on proportion of patients achieving clinical improvement defined as a two point reduction in six point ordinal scale from patients admission status or live discharge from the hospital, which ever came first.

**Results:** Baseline characteristics were identical in both R and RT group. Biomarkers, C reactive protein, IL-6 and serum ferritin levels were significantly more in RT group as compared to R group on day 1,3 and 7. But C reactive protein (CRP), serum ferritin and IL-6 levels from day 1 to day 7 gradually decreased in RT group and increased in R group.

**Conclusion:** In spite of higher levels of biomarkers morbidity and mortality of patients did not increase in RT group; use of tocilizumab might be responsible for the gradual reduction in the level of biomarkers in this group.

## KEYWORDS

COVID-19, SARS CoV2, Critical care unit, remdesivir, tocilizumab, efficacy

## INTRODUCTION:

Majority of the patients infected with severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) experience mild to moderate respiratory illness and recover without any special treatment. Only 5% patients become seriously ill and require hospitalization. Except glucocorticoids (GCs), there are still no really effective therapies for coronavirus disease 2019 (COVID-19)[1].

Remdesivir was found to be a potent inhibitor of SARS-CoV-2 replication in human nasal and bronchial airway epithelial cells. This outcome encouraged its use in patients with SARS CoV 2 infection (COVID 19), in the absence of any effective treatment.

Tocilizumab (TCZ), may be effective in reducing the severity COVID-19 infection and associated complications.[2]

Objective of this study was to find out the effect of adding tocilizumab to remdesivir on morbidity and mortality of COVID-19 positive patients.

This clinical trial might draw inferences from real clinical settings and serve effectively in near future. This might add to our collective understanding of this pathogen and therapeutic armamentarium against this virus in future.

## Methods:

After obtaining approval from institutional ethics committee, the study protocol was registered in the Clinical Trial Registry, India. This randomized open-level clinical trial was performed from December 2020 to February 2021 in a tertiary care hospital.

Laboratory confirmed moderate to severe COVID-19 patients of more than 18 years of age, admitted in critical care unit (CCU) with $SpO_2$ ≤94% on different modalities of oxygen therapy were included in this trial. Patients having acute respiratory distress syndrome (ARDS) /acute respiratory failure, those with radiologically confirmed pneumonia and raised inflammatory markers (CRP, ferritin, IL-6) were also included in this trial.

Pregnancy and breast feeding mothers; patients with known severe renal impairment (GFR <30 ml $min^{-1}$ 1.73 $m^2$ or on continuous renal replacement therapy) or raised serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level to > five times the upper limit of normal (ULN); patients on immunosuppressive or immunomodulatory therapy during last three months or absolute neutrophil count (ANC) <1000 cells/uL ; patients with clinical evidence of active tuberculosis and allergic to study drugs were excluded from trial.

For sample size calculation, a pilot study was conducted with six patients in each arm who received remdesivir and remdesivir plus tocilizumab respectively. The primary outcome was taken as death. It was observed that three patients (50%) who received remdesivir only died and one patient (15%) who received remdesivir + tocilizumab expired within 28 days. Considering 95% confidence interval and 80% power, based on the formula of the sample size of difference between two proportions (ref. https://select-statistics.co.uk/ calculators/ sample-size-calculator-two proportions/) , the sample size came as 25 in each arm.

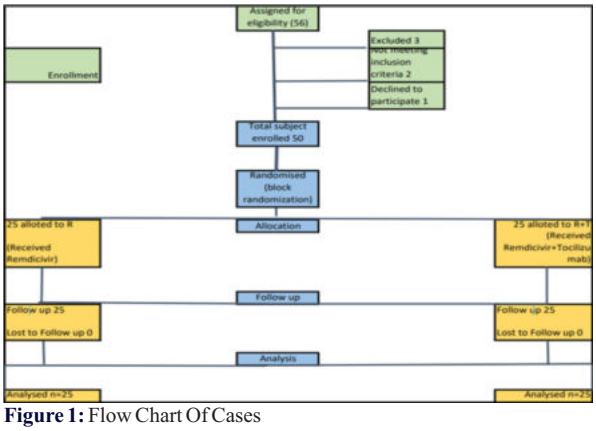


**Figure 1:** Flow Chart Of Cases

On admission at critical care unit, fifty six (56) patients were assessed for eligibility, three (3) were excluded, two (2) patients didn't met inclusion criteria, one (1) patient refused to participate. Finally, 50 patients were enrolled. Participants were randomized using computer generated block randomization scheduled in 1:1 allocation ratio to receive either injection remdesivir (group R) or injection remdesivir and tocilizumab (group RT) intravenously (vide figure 1: flow chart of cases). Allocation concealment was done by sequentially numbered opaque sealed envelope technique.

Patients allocated in the group 'R' received five days course of injection remdesivir: 200 mg intravenously on first day, followed by 100 mg IV daily for the remaining four days.

Patients belonging to group RT also received five days course of injection remdesivir: 200 mg intravenously on first day, followed by 100 mg of same drug intravenously daily for the remaining four days. These patients also received injection tocilizumab 400 mg IV on first day, which might be repeated after 12 hours if initial response was poor. Injection tocilizumab 400 mg was diluted in 100 ml of 0.9% Normal Saline and slowly infused over a period of one hour.

Oxygen therapy (non-rebreathing mask, high flow nasal canula, non-invasive and invasive ventilation) and other supportive therapy (corticosteroid like dexamethasone, methyl prednisolone; low molecular weight heparin as venous thromboembolism prophylaxis) were administered to both groups of patients. They were closely monitored for early identification of warning signs and further management.

Patients were assessed using daily record sheets capturing data which included the National Early Warning Score (NEWS) 2 ; the six-category ordinal scale [1: Discharged or having reached discharge criteria ; 2: Hospital admission, but not requiring oxygen therapy ; 3: Hospital admission for oxygen therapy (but not requiring high flow or non-invasive ventilation) ; 4: Hospital admission for non-invasive ventilation or high flow oxygen therapy ; 5: Hospital admission for mechanical ventilation or ECMO; 6: Death] and safety profile [daily monitoring of vital signs, presence of any adverse events (nausea, vomiting, dyselectrolytemia, hypotension, acute kidney injury, hepatic impairment, oral fungal infection, CCU psychosis)]; laboratory testing (day-1,3,7, 10) and, 12 lead ECG (day-1, 14) from day-1 to day-28 or discharge or death. Other clinical data were recorded using the WHO International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) case record form.

Discharge criteria were: 1. Afebrile for ≥3 days; 2. Respiratory rate <24/min; 3. SpO2 >94% in room air 4. No respiratory tract symptoms like cough, shortness of breath etc.

Inflammatory markers such as serum CRP, ferritin, D-dimer and, IL-6 were estimated on day-1, day-3 and, day-7 for evaluation of treatment response in both groups.

Other parameters which were also noted in both the groups of patients were : 1. Time from symptom onset to starting study treatment; early (<10 days) Vs late (>10 days) from admission ; 2. Patients receiving vasopressor or not ; 3. Comorbidities – heart disease /liver disease (Serum AST and ALT <1.5 times ULN)/ hypertension / diabetes mellitus / chronic kidney disease (eGFR >30 ml/min/1.73 $m^2$) ; 4. Modalities of oxygen therapy : non-invasive Vs invasive ventilation ; 5. Use of antibiotics ; 6. Use of corticosteroids ; 7. Inflammatory markers (Serum CRP, ferritin, D-dimer, IL-6)

Primary endpoint with respect to the efficacy of the drug (either remdesivir alone or remdesivir plus tocilizumab) in moderate to severe COVID-19 patients was the proportion of patients achieving clinical improvement defined as a two point reduction in six point ordinal scale from patients admission status or live discharge from the hospital, which ever came first.

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and Graph Pad Prism version 5. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. p-value ≤ 0.05 was considered for statistically significant.

**RESULTS:**

**Table 1: Baseline Characteristics And Laboratories Parameters Of Two Groups Of Patients**

| Baseline Parameters | | Remdesivir | Remdesivir+ Tocilizumab | P value (Chi square) |
|---|---|---|---|---|
| Age in Years | Median (IQR) | 60 (47-69) | 57 (49.5-64.5) | 0.554 |
| Gender | Male | 16 (64%) | 17 (68%) | 0.765 |
| | Female | 9 (36%) | 8 (32%) | |
| Presence of co-morbidity | Nil<br>One<br>More than one | 2 (8%)<br>8 (32%)<br>15 (60%) | 3 (12%)<br>5 (20%)<br>17 (68%) | 0.601 |
| Time since symptoms appears(days) | Median (IQR) | 9 (7.5-11.5) | 10 (9-12) | 0.144 |
| $SpO_2$(%) | Median (IQR) | 89 (86-93.5) | 89 (79.5-92) | 1.000 |
| Systolic blood pressure (mmHg) | Median (IQR) | 140 (129-149) | 140 (120 -150) | 1.000 |
| Laboratories parameters | | | | |
| WBC count (cells/$mm^3$) | Median (IQR) | 9800 (7950-11794) | 9258 (7520-11767) | <0.0001 |
| Lymphocyte (cells/$mm^3$) | Median (IQR) | 719(639.5-778) | 781 (662-11767) | 0.1094 |
| Platelet count (cells/$mm^3$) | Median (IQR) | $2.65X10^5$ ($1.81X10^5$-$3.28X10^5$) | $1.82X10^5$ ($1.68X10^5$-$2.03X10^5$) | 0.6946 |
| Urea(mg/dL) | Median (IQR) | 30(28-38) | 38(31.5-42) | 0.3319 |
| Creatinine (mg/dL) | Median (IQR) | 0.8 (0.74-0.9) | 0.9 (0.82-1.0) | 0.9388 |
| SGPT(U/L) | Median (IQR) | 40 (38-44) | 43 (41-44.5) | 0.7419 |
| SGOT(U/L) | Median (IQR) | 34 (28-44) | 42 (40-45)) | 0.3587 |
| LDH(U/L) | Median (IQR) | 340 (308-340.5) | 674 (463-826.5) | <0.0001 |

**Abbreviations:** U/L- unit/liter; SGPT- Serum Glutamic Pyruvic Transaminase; SGOT - serum glutamic-oxaloacetic transaminase; LDH - lactate dehydrogenase; IQR - interquartile range

A total of 50 patients were enrolled in the study amongst which 25 received remdesivir and another 25, remdesivir plus tocilizumab. Baseline parameters such as age, gender and presence of co-morbidity were comparable between the two groups of patients (table 1). Median time for CCU admission after appearance of COVID symptoms was nine and ten days in R group and RT groups respectively.

There was significant improvement of platelet count and serum LDH level on Day 10 of treatment in the R and RT group. Other parameters did not differ significantly among the two groups.

**Table 2: Treatment Related Statistics Among Two Study Groups (Chi Square Test)**

| Treatment received | | Remdesivir | Remdesivir+ Tocilizumab | P value (Chi square) |
|---|---|---|---|---|
| Antibiotic | Ceftriaxone + Doxycycline | 11 (44%) | 9 (36%) | 0.2 |
| | Piperacillin + Tazobactum + Doxycycline | 11 (44%) | 13 (52%) | |
| | Meropenem + Doxycycline | 3 (12%) | 3 (12%) | |
| Steroid | Dexamethasone | 21 (84%) | 22 (88%) | 0.683 |
| | Methyl Prednisolone | 4 (16%) | 3 (12%) | |
| Vasopressor | Given | 1 (4%) | 3 (12%) | 0.297 |
| | Not given | 24 (96%) | 22 (88%) | |

| | | | | |
|---|---|---|---|---|
| Type of oxygen therapy | NRBM | 0 | 1 (4%) | 0.7851 |
| | HFNC | 16 (64%) | 16 (64%) | |
| | Non-invasive ventilation | 1 (4%) | 1 (4%) | |
| | Invasive ventilation | 8 (32%) | 7(28%) | |
| LMWH | Given | 25 (100%) | 24 (96%) | 0.3124 |
| | Not given | 0 | 1 (4%) | |

**Abbreviations:** NRBM – Non-rebreathing mask; HFNC – High flow nasal canula; LMWH – Low molecular weight Heparin

All patients of both groups received antibiotics doxycycline (table 2). In addition they also received either meropenem or ceftriaxone or piperacillin plus tazobactum. Majority of patients received dexamethasone as steroid. 21 (84%) patients in the "R" group and 22 (88%) patients of "RT" group received dexamethasone (0.2-0.4 mg / kg in two divided doses for 5-7 days) and 4 (16%) patients of "R" group and 3 (12%) patients of "RT" group received methyl prednisolone (1-2 mg / kg in 2 divided doses for 3-5 days). In "R" group, 16 (64%) received HFNC, 1 (4%) received NIV and 8 (32%) received invasive ventilation. In "RT" group, 1 (4%) received NRBM, 16 (64%) received HFNC and 1 (4%) received NIV and 7 (28%) received invasive ventilation. Vasopressor was required in one patient in R and three patients in RT group. Invasive ventilation was required in eight and seven patients in R and RT group respectively.

All the differences were statistically significant in Day 1 and Day 3 among the two study groups (table 3).

In Day seven all the differences were statistically significant except serum ferritin.

**Table 3. Important Biomarkers Of COVID 19 Infection Measured On Day 1, Day 3 And Day 7 Among Two Groups (n=50)**

| | | Remdesivir | Remdesivir+ Tocilizumab | Remdesivir | Remdesivir+Tocilizumab | Remdesivir | Remdesivir+Tocilizumab |
|---|---|---|---|---|---|---|---|
| | | Day 1 | | Day 3 | | Day 7 | |
| CRP mg/L | Median | 23 | 78 | 25 | 67 | 32 | 49 |
| | Intra Quartile Range | 15-42 | 46-112.5 | 20-51.5 | 49.5-133.8 | 21-57 | 27-177.5 |
| Serum Ferritin ng/ml | Median | 370 | 657 | 409 | 612 | 398 | 444 |
| | Intra Quartile Range | 335-484 | 536.5-758 | 347-468 | 438-876.5 | 350-506 | 349.5-1325 |
| IL-6 pg/ml | Median | 116 | 798 | 189 | 677 | 212 | 397 |
| | Intra Quartile Range | 78-295 | 461-1289.5 | 83.5-321 | 416.5-2007 | 83-345 | 299.5-2015.5 |
| D-dimer µg/ml | Median | 3.20 | 0.95 | 2.91 | 1.2 | 2.8 | 0.75 |
| | Intra Quartile Range | 1.52-6.69 | 0.85-1.25 | 2.10-5.89 | 0.89-1.7 | 1.95-5.20 | 0.51-2 |

**Abbreviations:** CRP – C- reactive protein; mg/L – milligram / Liter; ng/ml – nanogram/Liter; pg/mL – picogram/milliliter ; g/mL – microgram/milliliter

Biomarkers C reactive protein, IL-6 and, serum ferritin levels were more in RT group on day 1,3 and 7 but, levels gradually decreased from day 1 to day 7. On the other hand, CRP, serum ferritin and IL-6 levels increased in R group. D-dimer level was lower in RT group. The incidence of secondary infection was not higher in the RT group.

Six point ordinal scale did not differ significantly among the two groups. (table 4 - Mann Whitney U Test)

**Table 4: Patients Status By Six-point Ordinal Scale On Day 21 (Mann Whitney U Test)**

| 6 point ordinal | Group | N | Mean Rank | Sum of Ranks | p value |
|---|---|---|---|---|---|
| Day 7 | Remdesivir | 24 | 26.96 | 647.00 | 0.311 |
| | Remdesivir+ Tocilizumab | 25 | 23.12 | 578.00 | |
| Day 21 | Remdesivir | 17 | 14.00 | 238.00 | 0.711 |
| | Remdesivir+ Tocilizumab | 11 | 15.27 | 168.00 | |

Probability of death was 1.185 times higher in R group than RT group though the difference was not statistically significant (table 5, p=0.085, Chi square test). Majority of patients recovered and were discharged from critical care unit.

**Table 5: Final Outcome Of The Two Groups Of Patients (chi Square Test)**

| S No | Final outcome | Remdesivir Group (No of patients) | Remdesivir +Tocilizumab Gr (No of patients) | Odds Ratio | p value |
|---|---|---|---|---|---|
| 1 | Death | 10 (40%) | 9 (36%) | 1.185 | 0.085 |
| 2 | Discharge | 15 (60%) | 16 (64%) | | |

Only 48% critically ill patients were discharged from CCU in R group while 56% patients were discharged in RT group within 20 days (table 6).

**Table 6: Number Of Patients Discharged From CCU (Critical Care Unit) After Recovery And Duration Of CCU Stay**

| Duration of stay (day) | Remdesivir Number of patients (%) | Remdesivir + Tocilizumab Number of patients (%) |
|---|---|---|
| 5 – 10 | 2 (8%) | 5 (20%) |
| 11 – 15 | 4 (16%) | 6 (24%) |
| 16 – 20 | 6 (24%) | 3 (12%) |
| >20 | 3(12%) | 2 (8%) |

**DISCUSSION:**

This randomized open-level clinical trial was performed from December 2020 to February 2021 in one of the tertiary care hospital among laboratory confirmed moderate to severe COVID-19 adult patients, and admitted in critical care unit with $SpO_2 \leq 94\%$.

Patients belonging to both R and RT groups were comparable in terms of demographic profile, clinical features and, associated co-morbid conditions. All patients received antibiotics and steroids as supportive therapy. Low molecular weight heparin was also administered in all patients except one in RT group. Supportive therapy was as per local guidelines. Hydroxychloroquine was not used in any patient as per WHO current recommendations. Oxygen therapy was required in all patients. Oxygenation was maintained in all patients either by non-rebreathing mask, high frequency nasal cannula, non-invasive ventilation or invasive ventilation.

Remdesivir is a pro-drug of an adenosine analogue with antiviral activity against a broad range of RNA virus families.[3],[4] The active analog inhibits viral replication by premature termination of RNA transcription in a broad range of viruses including corona virus. Ministry of Health and Family Welfare (MOHFW), Government of India recommended remdesivir in moderate to severe cases of

COVID-19 patients. In this trial remdesivir was used as per the recommendation of MOHFW[13].

Covid-19 is associated with deregulation of immune response and hyper inflammation. Higher levels of inflammatory mediators have been observed in Covid-19 patients. IL-6 is an important cytokine and is often raised in Covid-19 patients. Higher levels of interleukin-6 are positively correlated with critically ill Covid-19 patients and vice-versa. Tocilizumab, an anti-interleukin-6 receptor monoclonal antibody has been used for the treatment of Covid-19 patients with variable outcome. Previous workers used one or two doses of tocilizumab, 8 mg per kg of body weight intravenously.[5],[6] One or two doses of tocilizumab 400mg was used in this trial with remdesivir in RT group.

The 'Recovery' trial showed that in hospitalized COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved survival and other clinical outcomes regardless of the amount of respiratory support and was additional to the systemic corticosteroids[1].

Also the REMAP-CAP trial in critically ill patients found a significant reduction in 28-day mortality with tocilizumab[14].

In the present trial remdesivir was given to all patients of both groups. Administration of tocilizumab did not significantly change the outcome of patients in terms of mortality rate and duration of CCU stay in this trial. Rosas IO et al[7] also opined that tocilizumab plus remdesivir did not shorten the duration of hospital stay as compared to remdesivir plus placebo group. Carlos Salama et al[8] also observed no change in survival rate in patients receiving tocilizumab. Xavier Mariette et al[2] observed the beneficial effect of tocilizumab in Covid 19 patients. They opined that tocilizumab may be considered in patients with moderate to severe Covid-19 patients associated with pneumonia and raised CRP level.

Lakshmi Mahajan et al in their study on moderate to severe COVID-19 patients requiring CCU admission found that patients in the remdesivir group had a shorter time to improvement of one or two categories on the ordinal scale from baseline than patients in the non-remdesivir group[9].

Kapil Zirpe et al in their study on moderate to severe COVID-19 patients requiring CCU admission found that administration of tocilizumab in patients without intubation was associated with significantly lower mortality than those who required mechanical ventilation (62.5% vs. 4.8%, $P < 0.0001$)[10]

In the present trial, clinical parameters were comparable in two groups but, subsequently laboratories findings revealed significantly higher level of IL-6 level in RT group which, however, decreased from day 1 to day 7. Evidence suggests that elevated IL-6 serum levels is associated with increased mortality rates.[11],[12] Present study did not find higher incidence of complications or mortality in RT group. Outcome of patients in terms of mortality was better in this group (but statistically not significant, p value 0.085) in spite of higher IL-6 level. Limitation of the present study was relatively small sample size and short follow up duration.

## CONCLUSION:

The primary end point with respect to the efficacy of drug was improved in the RT group, though the difference was not statistically significant. In spite of higher levels of biomarkers, mortality and morbidity of patients did not increase in RT group. Based on the current results, remdesivir and tocilizumab given together may be promising agent as far as reduction of biomarkers are concerned for patients with moderate to severe SARS-COV-2 infection, if promptly initiated during the severe stage.

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