Low dose dexamethasone in combination with Remdesivir does not cause immune dysregulation

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Short Report

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Abstract

Background

The administration of Remdesivir/Dexamethasone combination on T and B cell responses in patients with COVID-19 is sparse. To compare cell mediated immune response in patients treated with only Remdesivir and Remdesivir/dexamethasone combination

Study Design

Prospective, cohort study

Methods

RT-PCR positive SARS-CoV-2 patients (n=49) were enrolled. Patients not requiring O2-supplementation were on remdesivir and those requiring were on remdesivir/dexamethasone. Baseline parameters (complete blood picture, inflammatory markers), T and B cells (flow cytometry: day 5 and 30) and neutralizing antibodies (chemiluminescence: day 30) were estimated. Students “t” test was used to evaluate the differences.

Results

Of the 49 patients, 26 (Mean age-44.68±13.45) were treated with remdesivir and 23 (Mean age-48.33±14.76) with remdesivir/dexamethasone combination. While blood counts and immune cells increased, inflammatory markers decreased post treatment in both the groups. A significant increase in WBC (6357±981Vs10700±1363; p=0.01), absolute neutrophil counts (4578±711Vs8256±1323; p=0.01) with decrease in levels of CRP (31±7.1Vs10±4.2; p=0.01), D-Dimer (172.3±8Vs118.1±12; p=0.0005), IL6 (17.6±3.8Vs1.72±0.2; p=0.0001), CD4 cells (2681±86Vs1256±369; p=0.0003), CD8 cells (1749±88 Vs 1256±221; p=0.01) and neutralizing antibodies were seen post treatment in the combination group. Correction of hypoxia and maintenance of oxygen >95% was also noted.

Conclusion

Remdesivir/dexamethasone combination given to patients requiring oxygen supplementation is safe at 4-6mg/day and showed a marked decrease in inflammation and no immune dysregulation.

Introduction

COVID-19, a severe acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2 resulted in unprecedented mortality worldwide [1]. Remdesivir is currently the only drug approved by FDA for the treatment of COVID-19[2] as it is demonstrated to reduce the viral loads invitro. Hospitalized patients with moderate COVID-19 receiving 5-day Remdesivir treatment revealed better outcomes than those on standard of care [3]. Further, ACTT-1 randomized clinical trial reported reduced time to clinical recovery in
severe COVID-19 patients [4] while there was no impact on 28-day mortality rate [5]. Dexamethasone a corticosteroid known for its anti-inflammatory and immunosuppressant effects [6] was shown to lower 28-day mortality in hospitalized patients needing mechanical ventilation [7] (recovery Trial). Since the pathogenesis of COVID-19 is established to be driven by viral replication early during the course and dysregulated immune response later in the course, a combination of antiviral and anti-inflammatory drug regimen might be beneficial for COVID-19 patients. However, safety and efficacy studies of combination of Remdesivir with Dexamethasone and the effect on immune responses have not been meticulously conducted in clinical trials [8]. Therefore, this study was taken up to assess the T and B cell responses in COVID-19 patients treated with a combination of Remdesivir and Dexamethasone.

Materials And Methods

Hospitalized COVID-19 patients (n=49) were enrolled in this single center, prospective, pilot study. Patients with comorbidities were excluded in order to avoid confounders. The study was approved by Institutional Ethics Committee of the Institute. All the participants had provided written informed consent. Whole blood was collected for assessing base line parameters (complete blood picture, inflammatory markers, T and B cell enumeration). Patients with hypoxia, shortness of breath and a CT severity score of > 10/25 (40% lung involvement) were administered either a combination of Remdesivir and Dexamethasone or only Remdesivir for those not requiring oxygen supplementation. Remdesivir was administered for 5 days; (day one 200 mg and day 2-5 100mg/day) and dexamethasone (4-6mg/ once daily) was given for 5 days in the combination group while in hospital. Post discharge 4mg dexamethasone once daily was continued for 7-15 days. Whole blood was collected for T and B cell enumeration at day 5 and 30 and neutralizing antibodies were tested on day 30. Patients were followed-up after discharge and for occurrence of any other infections due to immunosuppression for 3 months. Laboratory investigations and inflammatory markers were evaluated employing standard protocols. Peripheral Blood Mononuclear cells (PBMCs) isolated from whole blood were stained with a cocktail of surface antibodies that included CD3 (FITC), CD4 (Perp Cy 5.5), CD8 (APC-H7), for T-Lymphocytes and CD20(PE), for B-Lymphocyte (BD Biosciences, USA) and enumerated on flow cytometer ARIA II (BD Biosciences, USA). SARS-CoV-2 S1/S2 IgG neutralizing antibodies were enumerated as described earlier [9]. Of the 49 patients who were enrolled in the study, 23 (46.94%) patients received Remdesivir/Dexamethasone combination (Mean age: 48.33±14.76 years) and 26 patients (53.06%) received Remdesivir alone (Mean age: 44.68±13 years). There was no significant difference (p=0.36) in the mean age of the patients between the groups. Among the 23 receiving the combination, 13 (56.52%) were males (Age range: 22-72 years), 10 (43.48%) were females (Age range: 21-70 years) and among the 26 receiving only Remdesivir, 19 (73.08%) were males (Age range: 26-63 years) and 7 (26.92%) were females (Age range: 20-74 years). There was no significant difference in the numbers of males (p=0.41) and females (p=0.41) between the groups. Patients were discharged from the hospital on day 6 after treatment in both the groups. There was a significant difference in the numbers of individuals who were reported to have cough between individuals who were treated with the combination Vs those who were treated with Remdesivir alone (18 [78.26% Vs. 11 [42.31%]; p=0.01). However, the other clinical symptoms namely fever (18 [78.26%] Vs. 19 [73.08%]
p=0.67), Headache (5 [21.71%] Vs. 4 [15.38%]; p=0.56), Sore throat (4 [17.39%] Vs. 4 [15.38%]; p=0.84), Body pains (2 [8.7%] Vs. 5 [19.23%]; p=0.29), Hypoxia / Shortness of Breath (10 [43.48%] Vs. 7 [26.92%]; p=0.22), Anosmia and Dysgeusia (3 [11.54%] Vs. 3 [11.54%]; p=0.87), Cold (4 [17.39%] Vs. 3 [11.54%]; p=0.56), Nausea (3 [13.04%] Vs. 2 [7.69%]; p=0.53 and Fatigue/Generalized Weakness (8 [34.78%] Vs. 14 [53.85%]; p=0.18) were comparable between the groups.

Results

The total WBC, total lymphocyte and total neutrophil counts increased in both the groups post treatment (Figure 1A). While the levels of CRP, Ferritin, LDH, D-Dimer and IL6 decreased post treatment in both the groups, there was a relatively higher decrease (CRP: 3.1 Vs 1.82 fold, D-Dimer: 1.46 Vs 1.04 fold and IL6: 10.23 Vs 4.61 fold) in the Remdesivir/Dexamethasone combination as compared to only Remdesivir group. (Figure 1B). Furthermore, the immune cells namely CD3, CD4, CD8 and CD20 also showed an increased trend in both the groups with a comparatively higher increase in CD4 (1.98 Vs 0.81 fold) and CD8 cells (1.25 Vs 0.89 fold) in patients treated remdesivir and dexamethasone (Figure 1C). A higher neutralizing antibody response was noted in the remdesivir and dexamethasone group (120.74±26.13 Vs 69.98±11.75; p=0.07; Figure 1D).

One patient in the Remdesivir group was deceased on day 7 and none in the Remdesivir and dexamethasone group. All the patients given combination improved and maintained the oxygen saturation levels greater than 95%, 5 days’ post treatment. On follow up, at the end of 30 days, one patient in the Remdesivir and dexamethasone developed oral candidiasis and was managed with antifungal treatment. There was no evidence of mucormycosis in these patients after 3 months of follow up.

Discussion

In this pilot study, patients receiving combination of Remdesivir and dexamethasone did not show adverse effects due to administration of glucocorticoid suggesting that dexamethasone at this dose is safe in patients with COVID-19. Correction of hypoxia, maintenance of oxygen saturation >95%, decreased inflammatory markers and lower recovery time in patient requiring oxygen supplementation in the combination group demonstrates the efficacy of dexamethasone in the treatment of COVID-19. Although RECOVERY trial demonstrated lower 28-day mortality in hospitalized patients requiring oxygen support/mechanical ventilation, our study demonstrates that administration of glucocorticoid did not cause immune cell dysregulation. In conclusion our results demonstrate the safety and efficacy of Remdesivir and Dexamethasone treatment in Covid-19 disease. Hence the combination can be administered at this dose to Covid-19 patients with moderate disease requiring oxygen supplementation.

Declarations

Funding:
None

**Competing Interests:**

None declared

**Ethical approval:**

Obtained from the Institutional Ethics committee

**Disclosure:**

*Study design* – Sasikala Mitnala, Nageshwar Reddy Duvvur; *Data collection* – Kalyan Reddy Kannan, Kshiraja Damerla, Naveen Reddy, Nageshwar Reddy Duvvur; *Data analysis* – Sasikala Mitnala, Venkata Krishna Vemula; *Writing* – Sasikala Mitnala, Ravikanth Vishnubhotla.

All authors have approved the final article

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Figures

Figure 1

Blood Counts, Inflammatory markers, Immune cells and Neutralizing antibody levels in Remdesivir and Remdesivir and dexamethasone treated COVID-19 patients Panel A Shows Total WBC, absolute neutrophil and lymphocytes counts. A significantly higher total WBC counts post treatment with remdesivir (6060±639 Vs 9145±1034; p=0.01) and remdesivir and dexamethasone combination (6357±981 Vs 10700 Vs 1363; p=0.01) as compared to pre-treatment was noted. Likewise, Absolute neutrophil counts were also significantly higher pre and post treatment in both the treated groups.
(Remdesivir - 4233±608 Vs 6665±895; p=0.02 and Remdesivir/Dexamethasone - 4578±711 Vs 8256±1323; p=0.01). Absolute lymphocyte counts showed an increasing trend in the combination group, although not significant. Panel B shows inflammatory markers in the groups. A significant reduction post treatment as compared to pre-treatment in CRP levels (mg/L;31±7.1 Vs 10±4.2; p=0.01), D-Dimer (ng/ml; 172.3±8 Vs 118.1±12; p=0.0005) and IL6 (pg/ml; 17.6±3.8 Vs 1.72±0.2; p=0.0001) was noted with the Remdesivir and dexamethasone combination. Panel C shows numbers of immune cells in the groups. A significantly lower number of CD4 cells on Day 0 (2681±86 Vs 1256±369; p=0.0003) and day 5 (2733±100 Vs 1296±371; p=0.0003) in the remdesivir and dexamethasone combination as compared to numbers in the remdesivir treated patients was seen. Significantly lower numbers of CD8 cells in the combination group at day 0 was seen as compared to the only Remdesivir treated group (1749±88 Vs 1256±221; p=0.03). There was no significant difference in the numbers of CD3, CD4, CD8 and CD20 cells at day 30 in both the groups. Panel D shows neutralizing antibody levels in the group. A higher neutralizing antibodies was seen in the remdesivir/dexamethasone treated patients as compared to remdesivir alone (120.74±26.13 Vs 69.98±11.75; p=0.07). WBC- White Blood Cells; ANC – Absolute Neutrophil Count; ALC - Absolute Lymphocyte Count; CRP – C Reactive Protein; CD3 (cluster of differentiation 3); CD4 (cluster of differentiation 4); CD8 (cluster of differentiation 8); CD20 (cluster of differentiation 20)