

A Phase II Safety and Efficacy Study on Prognosis of Moderate Pneumonia in COVID-19 patients with Regular Intravenous Immunoglobulin Therapy

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The main finding of this study is that with IVIG treatment the duration of hospital stay was shorter and RT-PCR negativity was achieved early.

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ABSTRACT

Background: Currently, there is no specific drug for the treatment of COVID-19. Therapeutic benefits of intravenous immunoglobulin (IVIG) have been demonstrated in wide range of diseases. The present study is conducted to evaluate the safety and efficacy of IVIG in the treatment of COVID-19 patients with moderate pneumonia.

Methods: An open-label, multicenter, comparative, randomized study was conducted on COVID-19 patients with moderate pneumonia. 100 eligible patients were randomized in 1:1 ratio either to receive IVIG + standard of care (SOC) or SOC.

Results: Duration of hospital stay was significantly shorter in IVIG group to that of SOC alone (7.7 Vs. 17.5 days). Duration for normalization of body temperature, oxygen saturation and mechanical ventilation were significantly shorter in IVIG compared to SOC. Percentages of patients on mechanical ventilation in two groups were not significantly different (24% Vs. 38%). Median time to RT-PCR negativity was significantly shorter with IVIG than SOC (7 Vs. 18 days). There were only mild to moderate adverse events in both groups except for one patient (2%), who died in SOC.

Conclusions: IVIG was safe and efficacious as an adjuvant with other antiviral drugs in the treatment of COVID-19. The trial was registered under Clinical Trial Registry, India (CTRI/2020/06/026222).

Keywords: SARS-CoV-2, COVID-19, Immunoglobulin, IVIG, Pneumonia.

INTRODUCTION

The epidemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread all over the world and World Health Organization (WHO) declared the outbreak of coronavirus disease 2019 (COVID-19) a pandemic [1]. To date there are no specific medicines for COVID-19 patients. Interim results of WHO Solidarity Therapeutic Trial conducted on 11330 adults at 405 hospitals in 30 countries indicated that none of the four drugs (remdesivir, hydroxychloroquine, lopinavir-ritonavir, and interferon) showed little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients [2]. In a subsequent placebo-controlled study conducted on 237 severe COVID-19 patients, it was observed that another antiviral drug remdesivir was also not associated with statistically significant clinical benefits [3].

Due to lack of an effective antiviral agent, it is suggested to explore the efficacy of existing therapeutic products with acceptable safety profile. Intravenous immunoglobulin (IVIG) is one such blood product which is reported to have a wide range of therapeutic benefits in the treatment of variety of inflammatory, infectious, autoimmune and viral diseases [4]. IVIG has been shown to be particularly beneficial in the treatment of viral diseases such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and influenza. [5, 6, 7]. In view of these antiviral effects, in recent years, a number of studies evaluated the efficacy of IVIG in the treatment of COVID-19 patients [8]. In a multicenter cohort study, conducted at 8 centres on 325 adult critical patients, it has been shown that early (≤ 7 days) administration of high dose (>15 g/d) of IVIG improves the prognosis of critical type patients with COVID-19 [9]. In addition, a randomized, double-blinded study conducted on 59 patients with severe COVID-19 infection who did not respond to initial treatment, demonstrated that the administration of IVIG, in comparison to placebo, could improve the clinical outcome and reduce the mortality rate [10]. In another randomized, controlled study conducted on 33 COVID-19 patients, it was shown that IVIG significantly improved the hypoxia and reduced length of stay in hospital and progression to mechanical ventilation [11]. In a retrospective study conducted on 12 patients with severe COVID-19, clinical benefits including viral

clearance of IVIG have been demonstrated [12]. In view of these beneficial effects, use of IVIG is recommended in the list of selective methods in the COVID-19 therapeutic guidelines of WHO [13]. Immunoglobulin showed antiviral and anti-inflammatory effects through increasing certain cytokine secretions and hence, immunoglobulin is thought to be beneficial in the treatment of COVID-19 [9]. The rationale for undertaking the present study on the use of IVIG in patients with COVID-19 was that IVIG might provide immunomodulatory effect in hyperinflammation state, thereby providing therapeutic benefit. It is reported from China that more than 80% of COVID-19 patients are with mild to moderate disease [14]. Hence, the present study was initiated with the primary objective of finding out the safety and efficacy of IVIG in the treatment of COVID-19 patients with moderate pneumonia.

METHODS

This open-label, multi-centre, parallel group, randomized, safety and efficacy phase II study was conducted in accordance with principles under 1964 Declaration of Helsinki and later revisions, at 4 centers across four Indian cities, between July 2020 and September 2020. The study was initiated after obtaining approval from Indian Regulatory body - Drugs Controller General of India (DCGI) and institutional ethical committee at respective centers.

Eligible and consenting patients were randomized by block randomization in a 1:1 ratio to receive IVIG therapy + standard of care (Test group) or standard of care alone (Control group). After hospital admission, patients daily received immunoglobulin 0.4 g/kg body weight for 5 days. This dose was selected based on a publication by Reynaga et al [15]. Standard of care consisted of Azithromycin; Lopinavir/ritonavir; Piperacillin + Tazobactam; Acetaminophen and Pantocid. Patients with co-morbid diseases such as diabetes and/or hypertension were given appropriate treatment. Participants who met the following inclusion criteria were enrolled after obtaining informed consent: Male or female aged ≥ 18 years with RT-PCR confirmed COVID-19 illness; Patients with moderate pneumonia were defined as: body temperature $\geq 38.0^{\circ}\text{C}$ or $\text{PaO}_2/\text{FiO}_2$ 100-300 mmHg or respiratory rate $>24/\text{min}$ and oxygen saturation 90-93% on room air or lung involvement confirmed with chest X-ray. Patients with the following criteria were excluded: Viral pneumonia with other viruses besides

COVID-19; Patients with IgA deficiency or history of anaphylaxis to immunoglobulin therapy; Patients with severe pneumonia were defined as: respiratory rate ≥ 30 times/min or oxygen saturation $\leq 90\%$ in resting state or $\text{PaO}_2/\text{FiO}_2 \leq 100$ mmHg or respiratory failure requiring mechanical ventilation or Intensive Care Unit (ICU) monitoring with signs of other organ failure; Patients on either immunoglobulin or hydroxychloroquine treatment; Female patients who are pregnant or lactating. RT-PCR was measured based on real-time PCR technology for the qualitative detection of COVID-19 Viral RNA. Prothrombin time, lactate dehydrogenase, C-reactive protein and procalcitonin which are biomarkers of COVID-19 were measured using standard methodology.

Outcome measures:

The primary endpoint was number of days from initiation of treatment to hospital discharge. The secondary endpoints were: Time taken for improvement of clinical parameters which included number of days for normalization of body temperature ($<37^\circ\text{C}$), oxygen saturation ($>94\%$ on room air) and duration of cough; duration of mechanical ventilation from day 0 to 28; number of deaths during the follow-up of 28 days; proportion of patients with negative RT-PCR during the study period on day 14, on day 28 or end of the study period.

Statistical methods: The biostatistician generated random numbers using block randomization with block sizes of 4 using SAS program and allocated eligible patients either to Test group or Control group. Mean and SD values were calculated for quantitative variables and proportions were calculated for qualitative variables. Means were compared across groups by 't' test and violating the assumptions of homogeneity of variances or normality of the variables, non-parametric test of Mann Whitney 'U' test was used for demographic, vital, laboratory parameters, days for RT-PCR negativity, normalization of clinical parameters like temperature, respiratory rate, cough and oxygen saturation and duration of mechanical ventilation. Paired 't' test was used for mean comparisons over time for lab parameters and vitals for given groups. Chi square test was performed to study the association of groups and duration to attain RT-PCR negativity. Kaplan-Meier estimate was used to measure the

proportion of patients with positive RT-PCR for a certain time after treatment. Level of significance was considered as 0.05. SPSS windows version 24.0 was used for all statistical analyses.

RESULTS

103 patients who met the eligibility criteria were selected. However, 3 patients had withdrawn their consent after enrolment. The remaining 100 eligible patients were randomized into two treatment groups- Test group (n=50) and Control group (n=50). Intent-to-treat population consequently consisted of 100 patients, who received either one dose of study drug (IVIG) or SOC as stipulated in the protocol. Among them 33% of patients were females and 67% were males. The age of the participating patients ranged from 18 to 80 years and mean age was 48.7 ± 12.5 years. There were no statistically significant differences between the patients of the two treatment groups regarding age, gender, Body Mass Index and co-existing co-morbid conditions such as diabetes, hypertension and obesity between the two groups. Besides, there were no significant differences in hematological and biochemical parameters between the two treatment groups at the time of baseline (Table 1). While 96% of patients completed the study as per the stipulated protocol, 4 patients discontinued from the study. Among them one patient was lost to follow-up and three patients had treatment interruption and study withdrawal because of adverse events. The disposition of patients is presented in Figure 1.

Efficacy

The primary efficacy outcome was number of days hospitalized (from initiation of treatment day to discharge day). It was significantly ($P=0.0001$) lower in Test group as compared to that of Control group. Secondary efficacy outcomes, which reflected improvement of clinical parameters, included the following: Mean duration required to reduce the body temperature to $<37^{\circ}\text{C}$; normalization of oxygen; normalization of respiratory rate; mean duration for cessation of cough; mean duration of mechanical ventilation; length of stay in ICU. All these secondary efficacy variables, except for respiratory rate and number of days of stay in ICU, showed significant clinical improvement in Test group treated with IVIG ($P=0.005$) as compared to Control group treated with SOC alone (Table 2). Forty-six (92%) in Test group and 12 (24%) in Control group were RT-PCR negative at day 14. Six percentage of patients did not turn to RT-PCR negative with SOC alone at the end of 28 days. Hence, these were considered as treatment failure. On the other hand, none of the patients in IVIG group had

treatment failure. RT-PCR data for COVID-19, analysed by Kaplan-Meier curve, showed that Test group patients achieved early recovery as compared to Control group (Figure 2).

Safety

A total of 37 adverse events were reported by 27 patients throughout the study. In both treatment groups, maximum number of patients had mild – to - moderate adverse events such as dyspnea, swelling at infusion site, headache, and diarrhoea. Only one patient had a serious adverse event (death) in SOC alone group. While 17 adverse events were reported by 15 patients in Test group, 20 adverse events were reported by 12 patients in Control group. In addition, two patients (one patient due to tachycardia and another due to rashes) in Test group stopped medication due to adverse events. There were no significant differences between the groups in hematological and biochemical parameters at baseline and termination. However, Prothrombin Time (PT) and biochemical parameters such as Lactate Dehydrogenase (LDH), Alkaline phosphatase (ALP) and C-reactive protein (CRP) were significantly decreased from baseline to termination in both treatment groups.

DISCUSSION

In the present open-label, randomized, controlled study, the safety and efficacy of IVIG was evaluated in COVID-19 patients with moderate pneumonia. A total of 100 patients with RT-PCR confirmed COVID-19, were randomized in 1:1 ratio – 50 patients were assigned to the IVIG + SOC treatment (Test group) and 50 patients to the SOC treatment alone (Control group). The characteristics of the patients at baseline were generally balanced across the two groups (Table 1), thereby indicating effective randomization. Based on earlier experience of use of drugs in the treatment of Ebola and Severe Acute Respiratory Syndrome (SARS), standard of care of drugs in the present study were selected. This included antipyretic (Acetaminophen), antibiotics (Azithromycin, Piperacillin + Tazobactam), antivirals (Lopinavir/ritonavir), and antacid (Pantocid). COVID-19 patients with underlying diseases such as diabetes and hypertension, reported to have poorer clinical outcomes [16]. Therefore, these diseases were controlled with appropriate treatment in both Test and Control group. In recent years, a number of studies evaluated the efficacy of IVIG in the treatment of COVID-19 patients. [9, 10, 11].

Treatment with IVIG within 48 hrs of admission has not only reduced ventilator use, but also reduced length of stay in intensive coronary care unit ultimately lowering 28 day mortality. The study demonstrated that IVIG treatment in COVID-19 patients with severe pneumonia can improve the patients' clinical indicators within a short time and improve the treatment efficiency of the patients with high effectiveness [17]. Therefore, the present study was undertaken to evaluate the safety and efficacy of IVIG in COVID-19 patients with moderate pneumonia which might provide immunomodulatory beneficial effect in hyperinflammation state.

The results of this study have shown that initiation of IVIG as adjuvant treatment for COVID-19 patients with moderate pneumonia can reduce the number of days to clinical improvement, which is the primary endpoint. Besides, administration of IVIG to COVID -19 patients with moderate pneumonia can significantly reduce the following secondary endpoints: duration of use of mechanical ventilation; duration of hospitalization and length of stay in intensive coronary care unit from day 0 to 28. In addition, IVIG administration has also significantly increased the proportion of patients with negative RT-PCR on day 14. Analysis by Kaplan-Meier curve had shown that early recovery in RT-PCR negativity with IVIG treatment in Test group as compared to that with Control group, also led to a significantly shorter hospital stay for patients. Results of published studies as well as the present study show that immunotherapy with IVIG combined with antiviral drugs could provide an effective alternative treatment against COVID-19 [9, 10, 11].

In the present study, out of the 50 patients on IVIG, 15 patients reported 17 adverse events. On the other hand, 20 adverse events were reported by 12 patients in Control group. Thus, over all, 37 adverse events were reported by 27 patients in both groups. None of the patients had serious adverse events in Test group whereas one patient died in Control group. Adverse reactions to IVIG were reported to occur in less than 5 percent of patients [18]. All the reported events were mild -to - moderate in severity, which included headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea and hypotension [19]. In the present study, none of the patients discontinued the treatment due to adverse events in Control group whereas two patients discontinued the treatment in Test group. These results indicate that IVIG was well tolerated and safe in treatment of COVID-19

patients with moderate pneumonia. It is stated that IVIG tends to form aggregates which are believed to be responsible for the majority of the adverse effects [17]. Mild reactions to IVIG occurred within the first 30 min after infusion which was relieved by reducing the infusion rate or temporarily stopping the infusion.

In summary, initiation of IVIG as adjuvant treatment for COVID-19 patients with moderate pneumonia in combination with standard care of treatment, can reduce the use of mechanical ventilation, shorten the hospital length of stay, promote the early recovery of patients, and improve the effective treatment of patients to achieve significant clinical efficacy. The limitations of the present study include open-label design and small sample size. Besides, follow-up of patients was not done after their hospital discharge.

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Foot Note:

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Conflict of Interest: Two of the Thummala C Raghuram and Vishaly T Aravinda are full-time employees of Virchow Biotech, India. The other six authors do not have any commercial interest relevant to the manuscript.

Data presented in this manuscript was not presented at any meeting.

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Table 1. Patients Demographic Characteristics and Co-morbid Conditions at Baseline (Mean $\pm$ SD)

	Test Group (N=50)	Control (N=50)	P-Values
Age(Years)	48.4 $\pm$ 11.6	49.0 $\pm$ 13.5	0.82
Males N (%)	14 (28%)	19 (38%)	0.28
Females N (%)	36 (72%)	31 (62%)	
Body Mass Index	28.5 $\pm$ 4.5	26.7 $\pm$ 7.7	0.14
Body temperature ($^{\circ}$ C)	37.8 $\pm$ 0.7	37.9 $\pm$ 0.7	0.63
Respiratory Rate (breaths/Min)	21.1 $\pm$ 3.0	21.3 $\pm$ 3.5	0.81
Oxygen Saturation (%)	95.1 $\pm$ 3.6	95.1 $\pm$ 3.1	0.97
Diabetes Mellitus N (%)	13 (26%)	14 (28%)	0.82
Hypertension N (%)	18 (36%)	13 (26%)	0.28
Obesity N (%)	8 (16%)	8 (16%)	1.0
Total Leucocyte Count ($\times 1000/\mu$ L)	8451 $\pm$ 2930	8433 $\pm$ 3234	0.977
Platelet Count ($10^3/\mu$ L)	2.5 $\pm$ 0.8	2.4 $\pm$ 0.9	0.540
Prothrombin Time (Sec)	15.5 $\pm$ 3.4	16.1 $\pm$ 3.2	0.341
C-reactive protein (mg/L)	24.1 $\pm$ 28.6	29.8 $\pm$ 29.7	0.970
Procalcitonin (ng/mL)	0.24 $\pm$ 0.21	0.24 $\pm$ 0.21	0.332
Lactate Dehydrogenase (IU/L)	401.7 $\pm$ 180.6	445.8 $\pm$ 216.7	0.541

Table 2: Primary and Secondary efficacy variables (Mean $\pm$ SD)

Efficacy Variable	n	Test Group	n	Control Group	P Value
Primary:					
Number of Days of hospitalization	47	7.72 $\pm$ 2.69	46	17.50 $\pm$ 5.01	0.0001
Secondary:					
Number of days for normalization of body Temp $<37^{\circ}\text{C}$	22	2.18 $\pm$ 1.87	11	5.45 $\pm$ 4.39	0.005
Number of days for normalization of oxygen	11	2.45 $\pm$ 1.63	12	4.75 $\pm$ 3.0	0.03
Number of days for normal respiratory rate	9	2.44 $\pm$ 1.81	12	5.45 $\pm$ 4.27	0.06*
Number of days for cessation of cough	23	3.52 $\pm$ 1.16	16	6.67 $\pm$ 2.29	0.0001
Number of days on mechanical ventilation	12	2.42 $\pm$ 0.9	19	4.47 $\pm$ 2.7	0.01
Number of days in Intensive Care Unit	2	4.0 $\pm$ 1.4	3	5.0 $\pm$ 3.0	0.69*

*Not significant

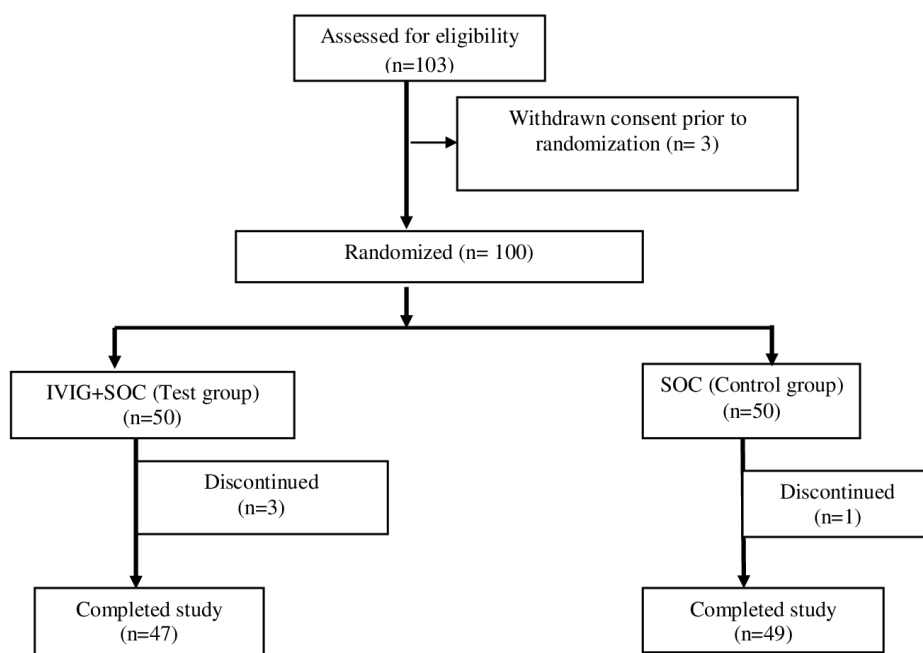


Figure 1. Disposition of patients

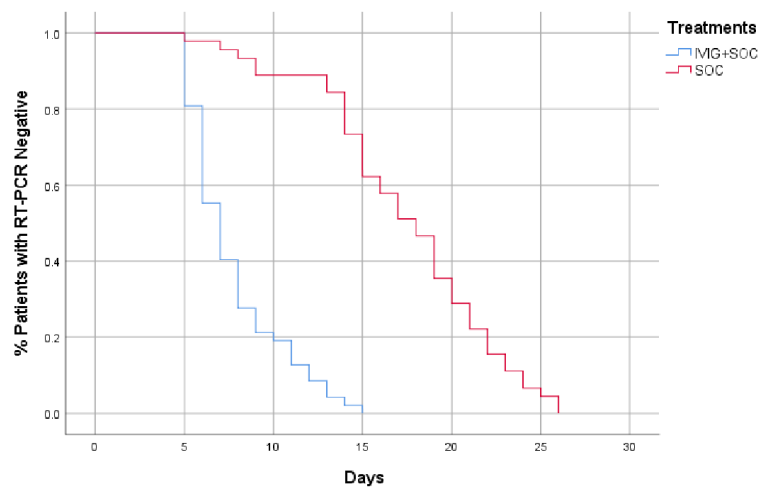


Figure 2. Percentage of patients with negative RT-PCR for COVID-19 from day 0 to day 28