Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1036274
J Health Sci Med 2022; 5(3): 794-798

Early and late results of intravenous immunoglobulin as potential adjuvant therapies in critically ill COVID-19 patients: a retrospective cohort study

Canan Gürsoy[1], Özge Oral Tapan[2], Emrah Doğan[3], Sinan Pektaş[1], Semra Gümüs Demirbilek[1]

[1]Muğla Sıtkı Koçman University, Department of Department of Anesthesiology and Reanimation, Muğla, Turkey
[2]Muğla Sıtkı Koçman University, Department of Chest Diseases, Muğla, Turkey
[3]Muğla Sıtkı Koçman University, Department of Radiology, Muğla, Turkey

Cite this article as: Gürsoy C, Oral Tapan Ö, Doğan E, Pektaş S, Gümüs Demirbilek S. Early and late results of intravenous immunoglobulin as potential adjuvant therapies in critically ill COVID-19 patients: a retrospective cohort study. J Health Sci Med 2022; 5(3): 794-798.

ABSTRACT

Introduction: Intravenous immunoglobulin (IVIG), which is one of the adjuvant therapy strategies, has been started to be used in critically ill COVID-19 patients due to its anti-inflammatory and immunomodulatory effects.

Material and Method: In our study, it was aimed to evaluate the effect of IVIG used in critically ill COVID-19 patients in the intensive care unit on early laboratory findings and late lung damage. Twenty-two critically ill COVID-19 patients who met the inclusion criteria were included in the study. Laboratory data of the patients who received 0.4 gr/kg/day IVIG for 5 days were analyzed before the treatment and on the 1st and 5th days of the treatment. For the percentage of injured lung areas was evaluated with chest CT.

Results: Respiratory rate and CRP decreased with IVIG, while an increase was observed in PaO_2/FiO_2, WBC, lymphocyte count, D-Dimer and fibrinogen values, which was statistically significant ($p<0.05$). When IL-6 values before treatment and on the 3rd day of treatment were compared, it was observed that there was a statistically significant decrease ($p<0.001$). A statistically significant improvement in lung damage was found when the average percentage of injured lung area calculated from chest CT taken at hospitalization and 1 month after discharge was compared ($p<0.001$).

Conclusion: IVIG can be considered as an effective adjuvant therapy because it causes improvement in oxygenation, clinical symptoms and hyperinflammatory response. It should not be forgotten that it also provides improvement in the damaged lung areas in the late period.

Keywords: COVID-19, immunoglobulin, IVIG, pneumonia

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can be asymptomatic depending on the host's immune response and comorbidities, or it can cause life-threatening multi-organ dysfunction. In severe cases with refractory hypoxemia and developing acute respiratory distress syndrome (ARDS), mortality is determined by factors such as age, hypertension and chronic obstructive pulmonary disease, while the limited number of devices and intensive care beds in the health care system cannot meet the needs (1). In order to reduce the pressure of the disease on the health system, national and global vaccination programs have been initiated. Vaccination aims to reduce the severity of the disease and decrease mortality rates. Despite the rapid increase in vaccination rates all over the world, the emerging COVID-19 variants and the lack of effective treatment show that the pandemic remains serious. Today, while efficacy studies on vaccines continue, the role of adjuvant therapies such as convalescent plasma treatment, immunoglobulins, inflammatory modulators and stem cell therapies used against COVID-19 in the treatment is still being investigated (2).

Intravenous immunoglobulin (IVIG) has the ability to provide passive immunity against various pathogens and also can reduce the uncontrolled hyperinflammatory response against SARS-CoV-2 and inflammation-related lung damage by creating immunomodulation

Corresponding Author: Özge Oral Tapan, ozgeeoral@hotmail.com
Received: 14.12.2021 **Accepted:** 11.04.2022

in severely and critically ill COVID-19 patients (3). However, the routine use of IVIG in the treatment of COVID-19 is controversial due to the lack of adequate clinical studies.

In this study, we aimed to present the effect of IVIG therapy used in critically ill COVID-19 patients in the intensive care unit (ICU) on symptoms, laboratory findings and percentage of injured lung area (ILA).

MATERIAL AND METHOD

After obtaining approval from the Ethical Committee for Clinical Researches of the Muğla Sıtkı Koçman University (Date: 03/02/2021, Decision No: 3/V), patients who were followed up in the Intensive Care Unit due to COVID-19-related acute respiratory failure (ARF) and were treated with IVIG at a dose of 0,4 mg/kg/day for 5 days in the years 2020 and 2021 were included in the study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Medical records of 31 patients were reviewed retrospectively. Patients younger than 18 years of age, incomplete medical data and patients for whom 5-day IVIG treatment could not be completed were excluded (**Figure 1**).

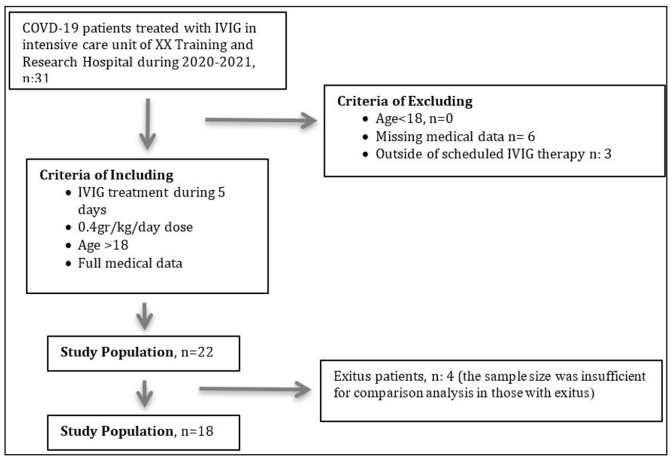

Figure 1. Flow chart displaying selective and exclusive process of patients with COVID-19 in the current study

Age, gender, APACHE II score, comorbidities, steroid use, presence of intubation, the day of initiation of IVIG treatment, number of days of hospitalization in the ICU and discharge status of the 22 patients included in the study were recorded. Before IVIG treatment, on the 1st, 3rd, and 5th days of the treatment, Sequential Organ Failure Assessment (SOFA) Score, the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FIO_2), respiratory rate (RR), white blood cell (WBC), lymphocyte, Lactate dehydrogenase (LDH), C-Reactive protein (CRP), D-Dimer, fibrinogen values were recorded. Interleukin-6 Cytokine (IL-6) values were noted before and on the 3rd day of treatment. All these data were considered as early results.

For late-term results, ILA percentages were calculated from thorax computed tomography taken at the time of admission to the ICU and 1 month after discharge. The percentage of ILA was calculated using chest CT taken during diagnosis of patients. Chest CT shots were obtained without contrast agent injection, during deep inspiration, in the supine position. The images were evaluated on a high-resolution medical screen. Three lobes on the right lung and 2 lobes on the left lung were examined separately. Each lobe was accepted by 20% and lobe volume was measured. The areas in the view of the consolidated and ground-glass area were calculated by volumetric voxel and calculated on the computer through the program. Their percentages were calculated over the total volume. The percentage values of all lobes were collected and total loss of lung aeration was found.

Statistical Analyses

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. While evaluating the study data, the distribution of the data was evaluated with the Shapiro-Wilk Test as well as the descriptive statistical methods (Mean, Standard Deviation, Median, Frequency, Ratio, Minimum, Maximum).

A total of 22 patients met the enrolment criteria of the study but the sample size was insufficient for comparison analysis in those with exitus. For this reason, comparison analyzes were made on living cases. The Friedman test was used for comparisons of quantitative data over three periods or more that did not show normal distribution. Wilcoxon test was used for comparison of the quantitative data between two periods that did not show normal distribution. Significance was evaluated at the $p<0.05$ level.

RESULTS

A total of 22 patients met the enrolment criteria of the study. The overall mortality was 18.18% (4/22) so 18 patients was evaluated after excluded exitus patients. The mean age of the patients was 53.64±11.75. Three (16.7 %) were females and 15 (83.3%) were males. Eight of the patients (38,9%) had no comorbidities. While 3 (16.7 %) of the patients were intubated, non-invasive mechanical ventilation, oxygen mask and/or high-flow oxygen therapy were used in 15 (83.3%) patients. (**Table 1**). The mean of APACHE II was calculated as 10.55±3.19 in the ICU hospitalizations of the patients (**Table 2**).

It was determined that steroids were used together with IVIG in the treatment of all patients. Dexamethasone was used in the treatment of 9 (40.9%) patients, and methylprednisolone was used in 13 (59.1%) patients. And patients received steroids for at least the duration of

IVIG therapy. Patients were treated with IVIG on average 8.95±3.39 days after the onset of the first COVID-19-related symptom. The duration of stay in the ICU was 14.9±10.85 days, and the duration of hospitalization was 26.62±20.74 days (**Table 2**).

Table 3 includes the data of the patients on the 1st, 3rd and 5th days of the treatment, and before IVIG treatment was started. While RR, SOFA, CRP values decreased with IVIG treatment, an increase was observed in PaO_2/FIO_2, white blood cell, lymphocyte count, D-Dimer and fibrinogen values, which was statistically significant ($p<0.05$). There was no statistical difference in lactate dehydrogenase and alanine aminotransferase values ($p>0.05$). While the mean of Interleukin 6 (IL-6) was 225.15±590.97 before IVIG treatment, it was calculated as 14,50±13,85 on the 3rd day of treatment, and this decrease in IL-6 was statistically significant ($p<0.001$) (**Table 4**). There were no complications associated with IVIG therapy in the patients.

When the average of the percentage of ILA calculated from the chest CT taken at the hospitalization and 1 month after the discharge was compared; It was determined that it regressed from 63.22 ±13.76% to 14.50 ±13.85%, and this improvement was found to be statistically significant ($p<0.001$) (**Table 5**).

Table 1. Demographic parameters of Patient (1)

	N (18)	%
Sex		
Female	3	16.7
Male	15	83.3
Comorbidity		
No comorbidity	7	38.9
Diabetes mellitus	2	11.1
Hypertension	4	22.2
Asthma	3	16.7
CAD	1	5.6
COPD	1	5.6
Steroids		
Dexamethasone	9	50.0
Methylprednisolone	9	50.0
Intubation		
No	15	83.3
Yes	3	16.7

CAD; coronary artery disease, COPD; Chronic obstructive pulmonary disease

Table 2. Demographic parameters of Patients (2)

	Mean ±Sd	Min-Max (Median)
Age	53.64±11.75	36-76 (52.5)
APACHE II	10.55±3.19	6-17 (9.5)
IVIG starting day	8.95±3.39	4-14 (8.5)
Length of stay in ICU	14.90±10.85	3-35 (11)
Length of stay in hospital	26.62±20.74	9-109 (22)

APACHE II; Acute Physiology and Chronic Health Evaluation II score, ICU; Intensive care unite

Table 3. Comparisons of SOFA and blood samples before IVIG treatment, 1st 3rd and 5th days of IVIG treatment

		Before IVIG	DAY 1	DAY 3	DAY 5	p-value
SOFA	Mean ±Sd Min-Max (Median)	4.33±0.77 4-6 (4)	3.94±0.73 2-6 (4)	2.89±1.57 1-8 (2)	1.83±1.1 1-4 (1.50)	0.001**
PaO_2/FIO_2	Mean ±Sd Min-Max (Median)	83.50±22.56 60-140 (77.50)	101±29.05 69-189 (94)	112.61±35.57 76-192 (107.50)	135.56±34.51 75-190 (140)	0.001**
RR	Mean ±Sd Min-Max (Median)	31.89±3.14 25-38 (32.50)	29.11±4.06 24-38 (28)	23.06±5.61 14-35 (22)	18.53±2.56 16-25 (18)	0.001**
WBC	Mean ±Sd Min-Max (Median)	11.56±4.41 4.72-22.12 (10.32)	11.67±3.99 4.12-21.9 (11.43)	10.82±3.42 6.83-23 (10.55)	9.27±3.51 5.55-21.9 (8.85)	0.029*
Lymp	Mean ±Sd Min-Max (Median)	0.64±0.22 0.29-0.95 (0.65)	0.66±0.27 0.21-1.41 (0.61)	0.9±0.38 0.48-1.98 (0.79)	1.02±0.36 0.37-2.06 (0.99)	0.001**
LDH	Mean ±Sd Min-Max (Median)	403.28±182.54 167-906 (363.50)	427.78±199.53 227-924 (374.50)	458.5±288.03 227 1403 (359.50)	490.39±370.28 190- 1661 (398.50)	0.721
ALT	Mean ±Sd Min-Max (Median)	52.72±44.54 13-198 (34.50)	52.56±52.06 17-246 (40)	55.50±47.65 19-197 (38)	59.22±42.91 24-170 (42)	0.777
CRP	Mean ±Sd Min-Max (Median)	107±80.39 20-327 (87)	92.87±67.12 9.6-246 (74)	63.43±40.82 8.78-143 (67)	47.33±58.35 4-257 (37.50)	0.001**
D-Dimer	Mean ±Sd Min-Max (Median)	732.78±570.54 144-1900 (683.50)	1106.10±1061.90 150-4073 (690)	1358.50±1093.7 269-4444 (880.50)	1434.94±1647.5 259-7412 (862)	0.012*
Fibrinogen	Mean ±Sd Min-Max (Median)	493.50±140.97 267-740 (528.50)	549.17±179.63 217-894 (550)	533.10±162.8 188 790 (521.50)	530.50±146.23 339-835 (500)	0.173

SOFA; Sequential Organ Failure Assessment Score, PaO_2/FIO_2; Pa02 to FIO_2 Ratio, RR; Respiratory Rate, WBC; White blood cell, Lymp; lymphocyte count, LDH; Lactate dehydrogenase, ALT; alanine aminotranspherase, CRP; C-reactive protein, * P-value<0.005, ** P-value<0.001

Table 4. Comparison of IL-6 value before and at the 3rd day of IVIG treatment

		Day 0	Day 3	p-value
IL-6	Mean ±Sd Min-Max (Median)	225.15±590.97 4.48-2503 (58.50)	156.44±295.3 1.36-1111 (31)	0.028*

IL-6; Interleukin 6, *P-value<0.005

Table 5. Comparison of ILA percentage in chest CT at the hospitalization to ICU and discharge from hospital

		Day 0 in ICU	Discharge Day	p-value
Percantege of ILA	Mean ±Sd Min-Max (Median)	63.22±13.76 40-80 (62)	14.5±13.85 0-40 (16)	0.001**

Percentage of ILA; percentage of injured lung area, ** P-value<0.001

DISCUSSION

The most effective treatment method has not been found for COVID-19, which has been affecting the whole world and increasing its pressure on health systems since December 2019. The failure of antiviral agents used in treatment has directed clinicians to use potential adjuvant therapies. IVIG is one of them and has been used in the treatment of COVID-19 due to its anti-inflammatory and immunomodulatory effects. There are different hypotheses regarding these immunomodulatory effect mechanisms (3). These are pathogenic antigen neutralization by divalent antibody fragments (F(ab)'2)-mediated mechanisms, immunomodulatory effects on endothelial cells and adaptive immune cells by fragment crystallisable (Fc)-mediated mechanisms, and immunomodulatory effects on other innate immune cells by Fc-mediated mechanisms (3). ((A) Neutralization of pathogenic antigens through the F(ab)'2-mediated mechanisms; (B) The immunomodulatory effects on endothelial cells through the Fc-mediated mechanisms; (C) The immunomodulatory effects on other innate immune cells through the Fc -mediated mechanisms; (D) The immunomodulatory effects on adaptive immune cells through the Fc-mediated mechanisms.) Although the molecular mechanisms for IVIG have been partially clarified, its role in the treatment of COVID-19 remains unclear. In this study, we evaluated in detail of the early clinical and laboratory data obtained during the treatment of COVID-19 patients receiving IVIG therapy.

It was observed that the PaO_2/FIO_2 ratios increased, RR decreased, and WBC, lymphocyte and CRP values decreased with high-dose IVIG treatment in our study. All values were analyzed before IVIG and on the 1st, 3rd and 5th days of treatment to emphasize the early results of IVIG treatment. In a prospective randomized trial, it was shown that there was an increase in PaO_2/FIO_2 and a decrease in the progression of mechanical ventilation requiring respiratory failure with IVIG treatment, and this was statistically significant in patients with an A-a gradient >200 mmHg (4). In this study, PaO_2/FIO_2 was evaluated on day 7. Herth et al. (5) emphasized that symptoms and laboratory findings improved with treatment in 12 cases they evaluated. This retrospective case series supports our study because it evaluated oxygenation simultaneously with treatment. Raman et al. (6) reported normalization in respiratory rate and oxygenation with IVIG. There are case reports in the literature in which IVIG was used in COVID-19 pneumonia and clinical improvement and improvement in oxygenation were observed (7-9). Although the results are promising, no data supporting the beneficial effect of IVIG use in COVID-19 could be obtained in the randomized controlled study of Tabarsi et al. (10). In the study, laboratory data were evaluated on days 0, 7 and 14, and no data on oxygenation was shared except for the need for mechanical ventilation. Secondary conditions occurring within the 14-day period may affect the laboratory data and cause different interpretation of the results (10). In our study, it was determined that the patients who received IVIG treatment had an improvement in oxygenation and respiratory rate. This situation can be considered as clinical improvement.

Theoretically, IVIG-related immunomodulatory effect occurs with high doses (3). Different doses of IVIG are used in studies in the treatment of COVID-19. In a multicentre retrospective cohort study conducted by Shao et al. (11), 28 and 60-day mortality was found to be lower in those who received IVIG higher than 15 g per day. However, high or low dose IVIG treatment had no effect on the number of days of hospitalization. In another study, it was reported that 20 g/day IVIG administration for 3 consecutive days may be effective and safe (12). In our study, high dose (0.4kg/kg/day) IVIG was administered to all patients for 5 days. In the study by Shao et al. (11), it was shown that the 60-day mortality decreased in those who started IVIG treatment within the first 7 days after hospital admission. There are also opinions that patients will not benefit much from IVIG treatment when systemic damage develops (13). In our study, the onset time of IVIG was 8.95±3.39 days after the onset of the first COVID-19-related symptom, and it can be said that IVIG treatment was started early.

The hyperinflammatory state resulting from the overproduction of proinflammatory cytokines such as IL-6 changes the prognosis of the disease (14). In our study, the IL-6 levels of the patients before IVIG treatment and on the 3rd day of treatment were compared and a statistically significant decrease was observed. According to our study results, it can be said that the hyperinflammatory state will decrease on the 3rd day of the treatment, and this may lead to positive results in the prognosis of the disease. Similar to our results, in a study comparing standard treatment and two groups using IVIG in addition to standard treatment, IL-6 levels were found to be lower in the group using IVIG (4).

In addition to the data evaluated during the treatment, the effect of IVIG use on late lung damage was also examined. A significant improvement was observed in the ILA percentages calculated from chest CT 1 month after discharge. Tabarsi et al. (10) evaluated 50% improvement in tomography on the 14th day of IVIG treatment, but they could not find a statistical difference. It is known that residual lung injury in post-COVID-19 syndrome continues even 4 months after clinical recovery (15). In this case, it may not be correct to associate the lack of improvement in the lung at the end of 14 days with IVIG treatment.

Our study has potential limitations. One limitation is the retrospective design of this study and the other limitation is the use of a single group and single ICU data. Despite the emphasis on the reduction in 28 and 60-day mortality with high-dose and early IVIG use (11), the relationship between IVIG and mortality was not evaluated in our study to avoid misinterpretation due to the low number of patients who died. This can be considered as a limitation.

CONCLUSION

As a result, IVIG can be considered as an effective adjuvant therapy in the COVID-19 pandemic, which could not be terminated despite the vaccines produced in a short time, because it causes improvement in oxygenation, clinical symptoms and hyperinflammatory response with high doses and early use. It should not be forgotten that it also provides improvement in the damaged lung areas in the late period.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Muğla Sıtkı Koçman University, Clinical Researches Ethics Committee (Date: 03/02/2021, Decision No: 3/V).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

REFERENCES

1. Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med 2020; 180: 1345-55.
2. Salian VS, Wright JA, Vedell PT, et al. COVID-19 Transmission, current treatment, and future therapeutic strategies. Mol Pharm 2021; 18: 754-71.
3. Liu X, Cao W, Li T. High-dose intravenous immunoglobulins in the treatment of severe acute viral pneumonia: the known mechanisms and clinical effects. Front Immunol 2020; 11: 1660.
4. Sakoulas G, Geriak M, Kullar R, et al. Intravenous Immunoglobulin (IVIG) significantly reduces respiratory morbidity in COVID-19 pneumonia: a prospective randomized trial. medRxiv 2020; 20157891.
5. Herth FJF, Sakoulas G, Haddad F. Use of intravenous immunoglobulin (Prevagen or Octagam) for the treatment of COVID-19: retrospective case series. Respiration 2020; 99: 1145-53.
6. Raman RS, Bhagwan Barge V, Anil Kumar D, et al. A Phase II safety and efficacy study on prognosis of moderate pneumonia in coronavirus disease 2019 patients with regular intravenous immunoglobulin therapy. J Infect Dis 2021; 223: 1538-43.
7. Çolak M, Kalemci S, Sarıhan A. Treatment of a case with COVID-19 administering intravenous immunoglobulin. J Glob Antimicrob Resist 2020; 24: 106-7.
8. Suzuki Y, Tanino Y, Nikaido T, et al. Severe coronavirus disease 2019 that recovered from respiratory failure by treatment that included high-dose intravenous immunoglobulin. Intern Med 2021; 60: 457-61.
9. Tatar E, Karatas M, Bozaci I, et al. Intravenous immunoglobulin and favipiravir treatment for a kidney transplant patient with severe COVID-19 pneumonia. Transfus Apher Sci 2020; 59: 1-3.
10. Tabarsi P, Barati S, Jamaati H, et al. Evaluating the effects of intravenous immunoglobulin (IVIg) on the management of severe COVID-19 cases: a randomized controlled trial, Int Immunopharmacol 2021; 90: 107205.
11. Shao Z, Feng Y, Zhong L, et al. Clinical efficacy of intravenous immunoglobulin therapy in critical ill patients with COVID-19: a multicenter retrospective cohort study. Clin Transl Immunol 2020; 9: 1-10.
12. Gharebaghi N, Nejadrahim R, Mousavi SJ, Sadat-Ebrahimi SR, Hajizadeh R. Correction to: The use of intravenous immunoglobulin gamma for the treatment of severe coronavirus disease 2019: a randomized placebo-controlled double-blind clinical trial. BMC Infect Dis 2020; 20: 1-8.
13. Cao W, Liu X, Bai T, et al. High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019. Open Forum Infect Dis 2020; 7: 1-6.
14. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host & Microbe 2020; 27: 992-1000.
15. Kamal M, Abo Omirah M, Hussein A, Saeed H. Assessment and characterisation of post-COVID-19 manifestations. Int J Clin Pract 2021; 75: 1-5.