Arch Iran Med. February 2021;24(2):139-143

doi 10.34172/aim.2021.22

http://www.aimjournal.ir

ARCHIVES OF IRANIAN MEDICINE

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Original Article

Infliximab and Intravenous Gammaglobulin in Hospitalized Severe COVID-19 Patients in Intensive Care Unit

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Abstract

Background: Severe coronavirus disease 2019 (COVID-19) may lead to the cytokine storm syndrome which may cause acute respiratory failure syndrome and death. Our aim was to investigate the therapeutic effects of infliximab, intravenous gammaglobulin (IVIg) or combination therapy in patients with severe COVID-19 disease admitted to the intensive care unit (ICU).

Methods: In this observational research, we studied 104 intubated adult patients with severe COVID-19 infection (based on clinical symptoms, and radiographic or CT scan parameters) who were admitted to the ICU of a multispecialty hospital during March 2020 in Tehran, Iran. All cases received standard treatment regimens as local protocol (Oseltamivir + hydroxychloroquine + lopinavir/ritonavir or sofosbuvir or atazanavir ± ribavirin). The cases were grouped as controls (n = 43), infliximab (n = 27), IVIg (n = 23) and combination (n = 11).

Results: There was no significant difference between controls and treatment groups in terms of underlying diseases or the number of underlying diseases. The mean age (SD) of cases was 72.42 (16.06) in the control group, 64.52 (12.965) in IVIg, 63.40 (17.57) in infliximab and 64.00 (11.679) in combination therapy; (P = 0.047, 0.031 and 0.11, respectively). Also, 37% in the infliximab group, 26.1% in IVIg, 45.5% in combination therapy, and 62.8% in the control group expired (all $P < 0.05$). Hazard ratios were 0.31 in IVIg (95% CI: 0.12-0.76, P = 0.01), 0.30 in infliximab (95% CI: 0.13-0.67, P = 0.004), 0.39 in combination therapy (95% CI: 0.12-1.09, P = 0.071).

Conclusion: According to the findings of this study, it seems that infliximab and IVIg, alone or together, in patients with severe COVID-19 disease can be considered an effective treatment.

Keywords: COVID-19, Infliximab, Intensive care units, Intravenous gammaglobulin

Cite this article as: Farrokhpour M, Rezaie N, Moradi N, Ghaffari Rad F, Izadi S, Azimi M, et al. Infliximab and intravenous gammaglobulin in hospitalized severe COVID-19 patients in intensive care unit. Arch Iran Med. 2021;24(2):139–143. doi: 10.34172/aim.2021.22.

Received: July 19, 2020, Accepted: October 28, 2020, ePublished: February 1, 2021

Introduction

Coronaviruses can cause a mild and limited infection in the upper respiratory tract, the gastrointestinal tract or the kidneys.[1] However, some of them, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome–related coronavirus (MERS-CoV), could also cause very severe illnesses.[2,3] In December 2019, a number of pneumonia cases were identified in Wuhan, China, for unknown reasons, leading to the identification of a new human coronavirus called coronavirus disease 2019 (COVID-19). This has become a global cause of concern and concern for the World Health Organization (WHO).[4-6]

Numerous evidences suggest that a subset of patients with severe COVID-19 may have the cytokine storm syndrome which may cause acute respiratory failure syndrome, and lead to death. COVID-19 mortality has been associated with high ferritin and IL-6, indicating that mortality may be due to virally driven hyperinflammation in several researches.[7,8] Therefore, in order to reduce mortality from the disease, the use of anti-inflammatory drugs with proven safety profile can be one of the treatment strategies.[7]

Intravenous gammaglobulin (IVIg) is isolated from human serum, and has a high level of polyclonal antibodies.[9] IVIg was first introduced in the 1970 as an immunomodulatory modifier with the potential to be used in all ages and for a long time.[10] The use of this drug has been previously suggested to treat and reduce the complications of the respiratory syncytial virus infection.[9] In addition, IVIg use has been reported in patients with

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acute respiratory distress from SARS-CoV in Singapore during 2003.[11] IVIg has also been used in COVID-19 patients in limited cases, and has shown beneficial effects.[12]

Infliximab, a chimeric monoclonal antibody (mouse Fv1, human IgG1) binds specifically to tumor necrosis factor-α (TNFα), thus preventing TNFα from binding to its receptors, and initiating intracellular signaling leading to gene transcription and further biological activity. Compared to corticosteroids, the use of TNF biological inhibitors has the potential to be a more specific and effective way to accelerate the recovery of severe alveolar damage that can occur due to infection with influenza, and coronavirus SARS viruses.[13] There are only very few studies about infliximab and COVID-19, and they suggest that infliximab may be effective in treatment of COVID-19.[14,15]

Until now, lack of specific treatment for coronaviruses, the high risk of death from infection with these pathogens, and the ability of these viruses to create an epidemic have been major problems in the treatment of these viral infections.[16] Currently, due to the worldwide spread of COVID-19, studies to identify appropriate treatments or reduce mortality in these patients are important goals. So, the aim of this observational study was to investigate the therapeutic effects of infliximab and IVIg administrations in patients with severe COVID-19 disease admitted to the intensive care unit (ICU) ward of a multispecialty hospital during March 2020, the first month of COVID-19 outbreak in Tehran, Iran.

Materials and Methods

In this observational research, we studied 104 patients over 18 years of age with severe COVID-19 infection (based on clinical symptoms and radiographic or CT scan parameters) who were intubated and admitted to the ICU of a multispecialty hospital in March 2020 (the first month of COVID-19 outbreak in Tehran, Iran).

Cases with symptom of tachypnea (respiratory rate > 35/min) and heart rate > 125 beat/min, and Spo_2 <85% on mask with reservoir, loss of consciousness, and unstable vital sign were intubated, and admitted to the ICU. All cases enrolled in the study had multilobar ground-glass opacities, and consolidations on chest computed tomographic (CT) scan.

According to the Iranian national and local guidelines of the multispecialty hospital up to the date, COVID-19 is treated using a standard treatment regimen based on the patient's condition: three-drug regimen (Oseltamivir + hydroxychloroquine + lopinavir/ ritonavir or sofosbuvir); or four-drug regimen (Oseltamivir + hydroxychloroquine + lopinavir/ritonavir or atazanavir + ribavirin or sofosbuvir),[17,18] which are used for all admitted patients including those in the control group.

Based on the physician's decision, patients received one of the standard treatment regimens mentioned earlier with or without one of trials therapy. Our aim in this study was to compare the outcome during hospitalization and hospital stay of patients between the control group and each of the trial groups.

In one group of patients (23 cases), IVIg was used as the trial therapy after intubation (IVIg 400 mg/kg/d slow infusion over 6 hours for 3 to 5 days). In another group of patients (27 cases), infliximab was used as the trial therapy after intubation (infusion of 5 mg/kg as a single dose in 350 ml of saline 0.9% serum injected intravenously over 3 to 4 hours slowly). In some cases, (11 cases), both IVIg and infliximab (combination therapy) were used as the trial therapy after intubation. All of these patients entered the study, and their information was collected in three separate groups as trials groups. Forty-three cases without any trial treatment were enrolled as the control group.

Then, the required information was collected from the patients' medical records. Data were analyzed use chi, independent *t* test and Mann-Whitney test to reveal the differences between two groups. The Kaplan–Meier method was used to calculate time-to-event outcomes for mortality from the time of ICU admission. Cox proportional hazards regression was used to investigate factors prognostic for the outcomes of interest. Statistical significance was defined as a P value ≤ 0.05 and all tests were two-sided.

Results

In our study, we assessed 104 cases including 43 cases as the control group and 61 cases in three trials groups; all patients were severe COVID-19 intubated patients admitted to the ICU. The demographic characteristics of the study groups are presented in Table 1. Out of all 104 cases, seven cases (6.7%) were smokers, four cases (3.8%) were hubble-bubble users, three cases (2.9%) were opium addicts, and two cases (1.9%) were alcohol users. There was no significant difference between controls, and each of trials recipients in terms of sex, smoking, addiction, hubble-bubble use, underlying diseases (Figure 1), number of underlying diseases, and type of standard treatment regimens (Figure 2). However, patients in the IVIg and infliximab groups were significantly younger than the control group (P = 0.047, and 0.031, respectively). In contrast, there was not any significant difference between mean age in the control group and the combination therapy group (P = 0.11, Table 1).

Duration of hospital stay and ICU stay in surviving and expired patients with variety of significance in surviving and expired patients between groups are presented in detail in Table 2. Twenty-seven cases (62.8%) in the control group, six cases (26.1%) in the IVIg group, ten cases (37%) in the infliximab group, and five cases (45.5%) in the combination therapy group expired (P = 0.009, 0.05, and 0.324, respectively, Table 2).

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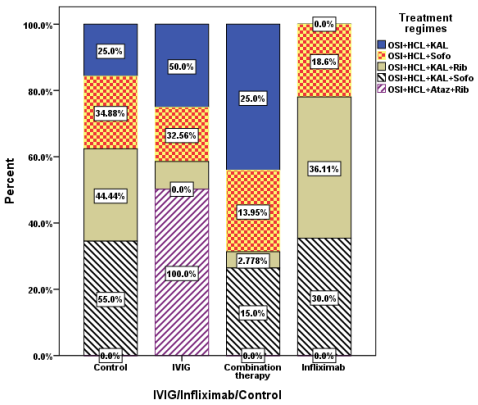

Figure 1. Treatment Regiments of Patients with Severe COVID–19 Disease Admitted to the Intensive Care Unit of the Multispecialty Hospital during March 2020.

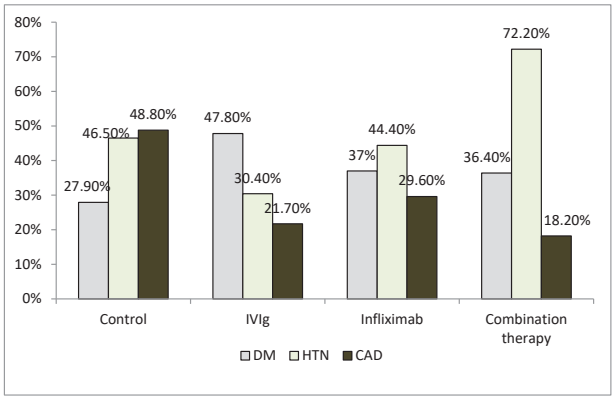

Figure 2. Underlying Diseases of Patients with Severe COVID–19 Disease Admitted to the Intensive Care Unit of the Multispecialty Hospital during March 2020.

ICU admission in the control group compared to each trial group are reported in Table 3. In Cox regression analysis, hazard ratios were 0.291 in IVIg (95% CI: 0.119-0.707, P = 0.006), 0.37 in infliximab (95%CI: 0.17–0.84, P = 0.017), and 0.29 in combination therapy recipients (95% CI: 0.11-0.78, P = 0.014; Table 4).

Discussion

Although the spread of COVID-19 has been very rapid all over the world during the past three months, our knowledge is still insufficient. Because specific treatments for the disease have not been identified, various therapeutic trials have been used around the world for these patients. In this study, we assessed the treatment outcomes of infliximab, IVIg or both of them together as a combination therapy in patients with severe COVID-19 who were intubated, and admitted to the ICU of a multispecialty hospital during March 2020. Because the time of treating these patients was the first month of coronavirus outbreak in Iran, there was not enough time and preparation for evaluation and necessary tests to examine patients before the trial. Based on this theory that some of the deadly complications of the COVID-19 are due to a cytokine storm,[7,8] infliximab and IVIg could alleviate and control this storm.[10,13-15] So, treatment with these agents was used as trials in our center by specialists who were involved with COVID-19 care (pulmonologists, and infectious disease specialists).

According to the findings presented in Table 1, there was no statistically significant difference between the study groups (control/infliximab/IVIg) in terms of gender, type, and the number of underlying diseases, and type of standard treatment regimens according to the regional protocol in our country. The infliximab and IVIg groups were younger than the control group, which was considered as a possible factor for confounding in subsequent analyses, and during the relevant analyses, its confounding effect was investigated and eliminated.

In this study, despite the improvement in survival and decreased mortality in all three groups, the length of hospital stay in the ICU or in ward was increased in groups who received infliximab with or without IVIg (with/without statistical significance, Table 2). This may be due to an increase in life expectancy in expired patients; but in improved cases, the same pattern was seen, which was

Table 1. Demographic Characteristics of Patients with Severe COVID-19 Disease Admitted to the ICU of the Multispecialty Hospital during March 2020

Characteristics		Control (43)	IVIg (23)	Infliximab (27)	Combination Therapy (11)
Age	Mean (SD)	72.42 (16.06)	64.52 (12.965)	63.40 (17.57)	64.00 (11.679)
	Median (Range)	75 (18–96)	63 (37–88)	63 (30–92)	64 (39–79)
	P value	—	0.047*	0.031*	0.11
Gender	Male	26 (60.47%)	16 (69.6%)	16 (59.3%)	10 (90.9%)
	Female	17 (39.53%)	7 (30.4%)	11 (40.7%)	1 (9.1%)
	P value	—	0.593	1	0.077
Number of underlying diseases[a]	Mean (SD)	1.30 (0.914)	1.09 (1.08)	1.15 (1.16)	1.36 (1.02)
	Median (range)	1 (0–3)	1 (0–3)	1 (0–3)	1 (0–3)
	P value	—	0.396	0.539	0.847
Treatment regimens	Triple drugs	18 (41.9%)	16 (69.6%)	8 (29.6%)	7 (63.6%)
	Quadruplet drugs	25 (58.1%)	7 (30.4%)	19 (70.4%)	4 (36.4%)
	P value	—	0.041*	0.324	0.310

*Statistically significant.

[a]Number of underlying diseases considered high risk for COVID–19 complications: Diabetes mellitus, Hypertension, Cardiovascular disease, Malignancy, Chronic obstructive pulmonary disease.

not investigated during this study. So, it is recommended that this should be carefully considered and examined in future studies.

The hazard ratios were 0.31 in IVIg, 0.30 in infliximab, and 0.39 in combination therapy recipients; this indicates that these drugs may be able to reduce mortality rate in these patients. Figure 3 confirms this, and the increase in survival after patients' admission to the ICU is quite evident in the all three groups.

Thus, infliximab, through its anti- TNFα effects, may help to control the cytokine storm and promote recovery in critically ill patients.[13-15] IVIg, through

Table 2. Outcomes of Patients with Severe COVID–19 Disease Admitted to the ICU of the Multispecialty Hospital During March 2020.

Outcomes		**Control (43)**	**IVIg (23)**	**Infliximab (27)**	**Combination Therapy (11)**
All cases	Discharge	16 (37.2%)	17 73.9%)	17 (63%)	6 (54.5%)
	Death	27 (62.8%)	6 (26.1%)	10 (37%)	5 (45.5%)
	P value	—	0.009*	0.05*	0.324
Surviving Cases		**Control (16)**	**IVIg (17)**	**Infliximab (17)**	**Combination Therapy (6)**
Hospitalization duration**	Mean (SD)	13.81 (6.794)	13.94 (6.179)	15.94 (7.66)	22.50 (5.891)
	Median (Range)	13 (5–30)	13 (6–25)	14 (7–37)	22.5 (15–31)
	P value	—	0.928	0.365	0.016*
ICU admission duration	Mean (SD)	5.62 (4.485)	7.29 (4.120)	9.76 (5.22)	14.50 (6.535)
	Median (Range)	4.5 (1–17)	5 (3–15)	7 (4–23)	14.5 (7–22)
	P value	—	0.145	0.006*	0.003*
Expired Cases		**Control (27)**	**IVIg (6)**	**Infliximab (10)**	**Combination Therapy (5)**
Hospitalization duration	Mean (SD)	7.44 (7.58)	9.17 (7.41)	13.50 (8.33)	16.80 (6.181)
	Median (range)	4 (1–28)	6 (3–23)	13 (3–27)	17 (7–23)
	P value	—	0.0249*	0.021*	0.015*
ICU admission duration	Mean (SD)	4.74 (4.16)	6.17 (3.061)	9.10 (6.136)	11.00 (3.391)
	Median (range)	3 (1–15)	5.5 (3–12)	7.5 (2–19)	11 (6–15)
	P value	—	0.137	0.031*	0.007*

*Statistically significant.
**Mann–Whitney test.

Table 3. Means and Medians for Survival Time in Patients with Severe COVID–19 Disease Admitted to the ICU of the Multispecialty Hospital During March 2020 (Log–Rank Test)

Survival Time in Patients with Severe COVID–19	**Mean**				**Median**				***P* value**
	Estimate	**Std. Error**	**95% Confidence Interval**		**Estimate**	**Std. Error**	**95% Confidence Interval**		
			Lower Bound	**Upper Bound**			**Lower Bound**	**Upper Bound**	
Control	7.289	0.960	5.408	9.170	5.000	1.437	2.183	7.817	—
IVIg	11.651	1.127	9.443	13.859	—	—	—	—	0.003*
Infliximab	15.120	1.630	11.926	18.314	15.000	1.679	11.710	18.290	0.001*
Combination therapy	15.602	1.936	11.807	19.398	15.000	2.640	9.825	20.175	0.007*

*Statistically significant.

Table 4. Cox Regression Analysis, Hazard Ratios for Patients with Severe COVID–19 Disease Admitted to the ICU of the Multispecialty Hospital During March 2020

Models	**Variable**	**Hazard Ratio**	***P* Value**
Control vs. IVIg	IVIg	0.31 (0.12 to 0.76)	0.010
	Hospitalization duration (<20 days vs. ≥20 days)	0.15 (0.04 to 0.52)	0.003
Control vs. infliximab	Infliximab	0.30 (0.13 to 0.67)	0.004
	Hospitalization duration (<20 days vs. ≥20 days)	0.16 (0.06 – 0.48)	0.001
	Coronary artery disease	2.40 (1.18 – 4.70)	0.015
	Age (<68 y vs. 68 y)	2.50 (1.07 to 5.75)	0.033
Control vs. combination therapy	Combination therapy	0.39 (0.12 to 1.09)	0.071
	Hospitalization duration (<20 days vs. ≥20 days)	0.09 (0.02 to 0.44)	0.003
	Hypertension	0.38 (0.17 to 0.85)	0.018
	Age (<68 y vs. 68 y)	2.42 (0.96 to 6.04)	0.058
	Smoker	5.72 (0.68 to 48.10)	0.108

immunomodulatory modifying or other potential effects,[10] could improve survival in our patients. One of the exciting findings was the improvement in survival in combination therapy recipients, who consisted of patients in very severe conditions and physicians chose to prescribe both drugs together. Similar to some reports on respiratory syncytial virus and SARS-CoV,[9-12] it may be stated the therapeutic results are encouraging in these patients, and they should be used as a treatment.

Therefore, according to the findings of this study, it seems that infliximab, IVIg and combination therapy in patients with severe COVID-19 disease can be considered as effective treatments. It is recommended that by controlling biomarkers, and evaluating the effectiveness of this treatment in terms of biomarkers in futures studies, the specific group of patients of patients who can have the most therapeutic effect are determined. In this way, these treatments may be administered more purposefully and also earlier, so that perhaps better treatment results are achieved in terms of reducing mortality and preventing intubation.

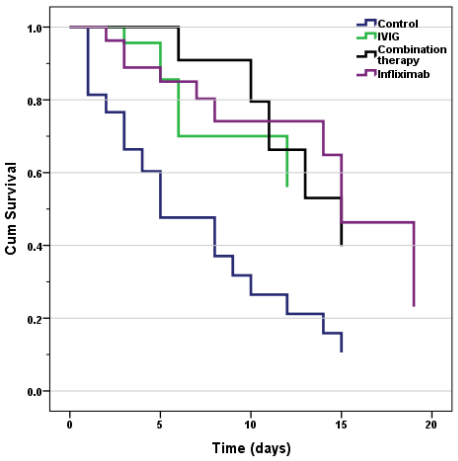

Figure 3. Survival of Patients with Severe COVID–19 disease admitted to the Intensive Care Unit of the Multispecialty Hospital During March 2020.

Authors' Contribution

MF, NR, NM, FGR, ShI, MA, MR, MJM, Al, MR, MY: Data collection. FZ, MY: study design and preparing condition. ShI, MY: Data analysis. MY, NM, ShI: Article writing.

Conflict of Interest Disclosures

Authors declare no conflict of interest.

Ethical Statement

This is an observational study, so after coordination with the relevant units in the hospital and using the patients' files without mentioning the names and details of patients was done.

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