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A Comparative Study of the Effects of Combination of Interferon-Gamma, and Vitamin C With Control Group (Kaletra) on the Recovery of Critically Ill COVID-19 Patients and Cytokine Storm

Sepideh Hassanpour Khodaei[1], Negin Hadisi[2], Shahram Dabiri[3], Mehdi Gharekhani[3], Hanieh Salehi-Pourmehr[4], Majid Shokoohi[3], Shahla Meshgi[5], Leila Roshangar[2*]

Abstract

Objectives: The COVID-19 pandemic has been a major global challenge since late 2019, leading to numerous deaths worldwide, primarily through the formation of cytokine storms. This study aimed to investigate the use of an anti-interferon-gamma antibody that targets both immunomodulation and macrophage enhancement to increase phagocytosis of the virus, reduce recovery time, and minimize side effects of the disease.

Materials and Methods: In an open-label, phase 2 trial, 60 patients with positive SARS-CoV-2 results were randomly divided into two groups. The Gamma-C group received three doses of interferon-gamma (IFN-γ) 200 mcg/0.5 mL (2 million I.U. per 0.5 mL) on alternate days, and one dose of vitamin C (500 mg/5 mL) every 8 hours for 7 days. The control group was treated with a routine protocol that included Kaletra (lopinavir 200 mg and ritonavir 50 mg), two tablets every 12 hours, and vitamin C (500 mg/5 mL) every 8 hours.

Results: The results showed a significantly reduced interleukin profile, rapid balancing of hematology and radiological results, no death outcomes, and a significantly shorter hospital stay compared with the control group.

Conclusions: This study highlights the potential of utilizing an anti-interferon-gamma antibody along with vitamin C supplementation as a treatment strategy for SARS-CoV-2 infection. The combination therapy demonstrated significant benefits, including reduced cytokine profile, rapid improvement in hematological and radiological parameters, absence of fatalities, and shorter hospital stays. These findings suggest the potential effectiveness of this approach in mitigating the severity and improving outcomes in COVID-19 patients.

Keywords: COVID-19, SARS-CoV-2, Interferon γ, Kaletra, Interleukin, TNF-α, Cytokine storm

Introduction

COVID-19 is an infectious disease that is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease is typically transmitted through droplets and physical contact (1). The COVID-19 virus is highly contagious and easily spreads from one person to another. Autopsy studies and animal models have shown that the disease primarily affects the lungs and can cause acute viral pneumonia, leading to respiratory failure (2). There is increasing evidence to suggest that a subset of individuals with severe COVID-19 may experience cytokine storm syndrome (3). Lymphopenia, characterized by significantly reduced levels of CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells, as well as decreased levels of monocytes, eosinophils, and basophils, are common symptoms in patients with severe COVID-19 but not in those with mild disease. An increase in the neutrophil count and the neutrophil-to-lymphocyte ratio often indicates the severity of the illness and predicts poor clinical outcomes. Additionally, markers of exhaustion, such as NKG2A, are upregulated on cytotoxic lymphocytes, including NK cells and CD8+ T cells, in patients with COVID-19 (4). Liu et al reported on the clinical features and cytokine profile of patients with severe COVID-19 in Wuhan, China. They proposed that a cytokine storm, indicated by elevated levels of granulocyte-colony stimulating factor, interferon gamma-induced protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1α, and tumor necrosis factor α, may be associated with disease severity (5). The pathophysiology of COVID-19 involves the release of a large amount of pro-inflammatory cytokines, including

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[1]Department of Dentistry, Eastern Mediterranean University (EMU) Famagusta, North Cyprus Mersin 10, Turkey. [2]Stem Cell Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. [3]Clinical Research Development Unit of Tabriz Valiasr Hospital, Tabriz University of Medical Sciences, Tabriz, Iran. [4]Research Center for Evidence-Based Medicine, Iranian EBM Center: JBI Center of Excellence, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. 5Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
*Corresponding Author: Leila Roshangar, Email: Lroshangar@yahoo.com

Key Messages

- COVID-19 reduced interleukin profile,
- COVID-19 led to rapid balancing of hematology and radiological results.

interferon (IFN)-alpha, IFN-gamma, IL-1-beta, IL-6, IL-12, IL-18, IL-33, TNF-alpha, and TGF-beta, as well as chemokines such as CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10. This cytokine and chemokine release is particularly evident in patients with severe disease (6). For many years, type I IFN-α/β have been investigated as agents that provide rapid innate antiviral protection (7). The use of anti-interleukin antibodies has been shown to decrease the severity of COVID-19 and reduce the mortality rate. Tocilizumab, a monoclonal antibody that targets the IL-6 receptor and modulates the immune response, is approved by the FDA for the treatment of rheumatoid arthritis and cytokine release syndrome following chimeric antigen receptor T-cell therapy. Hence, tocilizumab has been used in a small number of severe COVID-19 cases, with early reports suggesting success (8). A recent study has shown that the combination of interferon-beta and antiviral drugs leads to a significantly shorter time from the onset of study treatment to a negative nasopharyngeal swab (2). The point of this examination is to decide the optimal effects of IFN-γ immunotherapy on cytokine storm which previously had been proven in Ebola-infected mice (9).

Materials and Methods

Study Design and Patients

This was a phase 2, single-center, open-label, and randomized trial. Adult patients aged at least 32 years were admitted from July 31, 2020, to August 30 with COVID-19 positive test, and these patients were from the Ahar Bagher-Al-Olum Hospital. Inclusion criteria for the study were being at least 18 years old, having abnormal IL1, IL6, IL18, and TNF-a tests, CPK > upper limit of normal, high ferritin (Ferritin > 300 ug/L), SpO2 <93%, lack of a specific clinical disease such as immune system defects, and no pregnancy.

Randomization and Masking

Patients were randomly assigned to either the control group (Kaletra: Lopinavir/Ritonavir) or the combination of IFN-γ and vitamin C group, in the ratio of 1:1, by simple randomization with no stratification. Randomized treatment was open-label. Patients were assigned a serial letter from the resident doctor. Each serial letter was linked to the SAS software to assign the antiviral treatment regimens.

Procedures

In the combination group (IFN-γ and vitamin C) patients who were recruited and treated less than 7 days from symptom onset received a subcutaneous injection of one dose of IFN-γ 200 mcg/0.5 mL (2 million I.U. per 0.5 mL) on alternate days, and one dose of vitamin C (500 mg/5 mL) every 8 hours for 7 days. The patients in control group received only oral Kaletra (lopinavir 200 mg and ritonavir 50 mg) two tablets, every 12 hours, and vitamin C (500 mg/5 mL) every 8 hours. Due to drug interactions and the submitted Flowchart by the Deputy of Treatment, patients who received Kaletra have been given two tablets of Hydroxychloroquine sulfate 200 mg, once on the first day (as a single dose). For the individuals who created expanded alanine transaminase of three at least multiple times the upper limit of normal, the Kaletra treatment was decreased to once every day. The treatment of intercession must had been begun within 48 hours after medical hospital confirmation. In case of intolerance to gastrointestinal complications, having a history of heart arrhythmia disorders, or a high risk of drug interactions, using atazanavir/ritonavir was preferable over Kaletra. All patients had been given azithromycin 500 to prevent secondary bacterial infection, one dose every day. Patients who developed oxygen desaturation and required oxygen support had been given stress doses of corticosteroid or methylprednisolone (50 mg hydrocortisone, 500 mg methylprednisolone every 8 hours intravenously, tapering over 7 days).

Clinical and Laboratory Monitoring

History of disease, physical examination, laboratory tests, and radiological investigation results were collected and registered into a predesigned database. Chest radiography was taken on the admission day and high-resolution CT was done at the consultants' discretion on days 1 and 7 onset clinical trial. Patients who had the earliest negative test and stable laboratory tests were followed up 7 days after discharge by telephone call to evaluate their physical health. All recruited patients had been evaluated for the E gene by RT-PCR for detection of infection of SARS-CoV-2 in the nasopharyngeal swab. Due to the lack of kit, the final test for detection of viral load was taken only when patients achieved normal serological and hematological tests. Complete blood cell count (CBC) and Differential count (Diff) test, liver and renal function tests, lactate dehydrogenase, creatine kinase, and C-reactive protein (CRP) were checked regularly on days 1, 3,7, and 14 (up to day 20 for the control group), and the interleukin profile was checked on days 1 and 7.

Statistical analysis

Microsoft Excel version 2016, GraphPad Prism version 8.4.3, and Origin 2018 version b9.51.195 were used for statistical analysis. All quantitative analyses were represented by the mean or median (IQR). Means for continuous variables were compared using independent group *t* tests when the data were normally distributed, confidence interval (CI) and significance were set as a *P*

value < 0.05 for each group; otherwise, the Mann-Whitney U test was used. Also, the ANOVA test was performed for comparison of the mean among several independent groups, and the F statistic was reported for the ratio of changes between groups to within groups. The required example size has been determined to be 30 patients for each gathering to distinguish such a distinction at a two-sided α level of 0.05, with 80% power.

Results

Between July 31 and August 30, 2020, 60 patients were recruited (Figure 1). Figure 1 shows that the mean age was 51.5 years (IQR 25–80). Meanwhile, 32 (53.33%) patients were men and 28 (46.67%) women. Furthermore, 33 (50%) patients had underlying diseases. Among the 60 patients, 30 were randomly assigned to the IFN-γ and vitamin C group (combination), and 30 patients were allotted to the Kaletra (control) bunch. Inside the amalgamation bunch, 30 patients were admitted to the hospital under 7 days from the indication beginning and got the IFN-γ and vitamin C routine, and 30 patients who were conceded 7 days or more after the beginning of side effect got the Kaletra and Hydroxychloroquine ordinarily. Among 60 patients, 20 were hospitalized in the intensive care unit (ICU) and among these 20 patients, 17 were given IFN-γ and 3 had declined the IFN-γ treatment. The mortality rate of 30 days and intubation were 3 within the control group. There was no death or intubation by combination group. The mean of received doses of IFN-γ was three within five days. The mean time of hospital stay of the IFN-γ -C group was 8 (8-12) and for the control group was 18 (13-26) days. All the IFN-γ group patients had been discharged 8 days after the onset of the trial (CI: -11.59 to -8.517; $P < 0.0001$). The mean time of hospital stay from symptom onset to the start of treatment was 3 days (1-7) for the IFN γ-C group and 4.5 days (1-7) for the Kaletra (CI: 0.1865 to 1.747, $P = 0.0161$).

Fever, body aches, and cough were the most common presenting signs and symptoms. Also, 18 women complained of menstrual difficulties and abnormal uterine bleeding such as menorrhagia, metrorrhagia, hypermenorrhea, and perceptible change in blood color too dark. Most patients had thrombocytopenia, lymphopenia, increased CRP, and high lactate dehydrogenase (LDH) levels. Likewise, IL1B, IL6, IL18, and TNF-α were significantly high in both groups. The first noteworthy changes were for the interleukin profile. IFN γ-C group had a significant decrease (Figure 2). IL1B mean level had dropped down almost >×3 of the control group, whereas the control group had a slight increase in mean level after 7 days (F: 3.450, $P < 0.0190$). Likewise, IL6, TNF-α, and IL18 for the IFN-γ group had drastic reduction (F: 17.67, $P < 0.0001$; F: 38.14, $P < 0.0001$; F: 39.60, $P < 0.0001$ respectively), but the control group had a slightly increased mean level of both IL6 and TNF-α ($P = 0.4991$; $P < 0.9028$ respectively). IL18 within the control group decreased slightly ($P = 0.9028$). The second significant outcome was the increased mean levels of lymphocytes. IFN γ-C group had experienced 3× and the control group >1× raised levels of lymphocyte within 7 days (F: 150.6; $P < 0.0001$). Also, platelets had a significant rise in IFN γ -C group, whereas the control group had no significant change (F: 57.38; $P < 0.0001$) (Figure 3). Table 1 presents hematology and serology results, while Table S1 (Supplementary file 1)

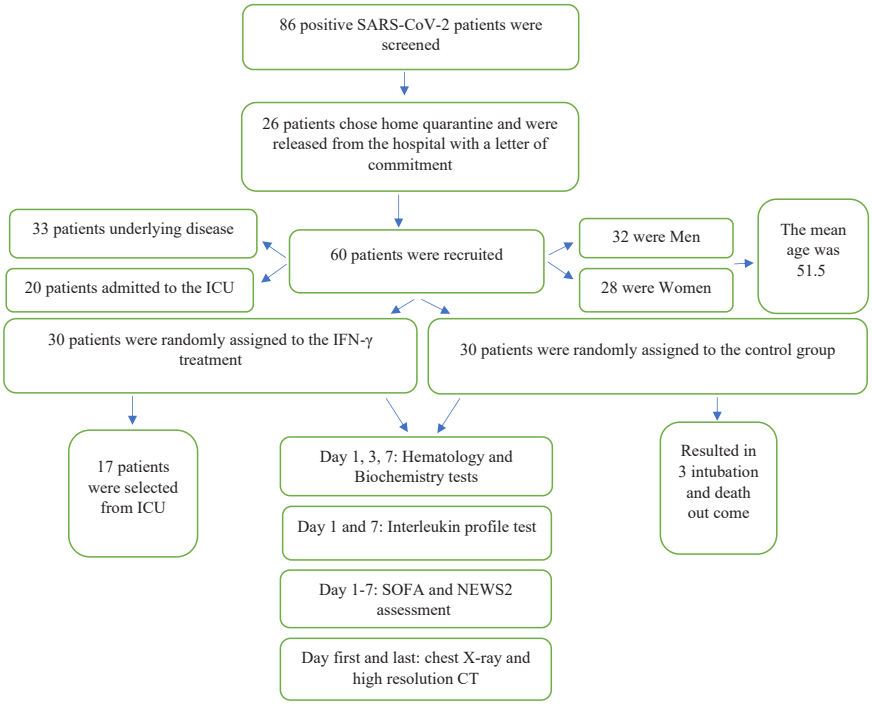

Figure 1. Study Design and Groups.

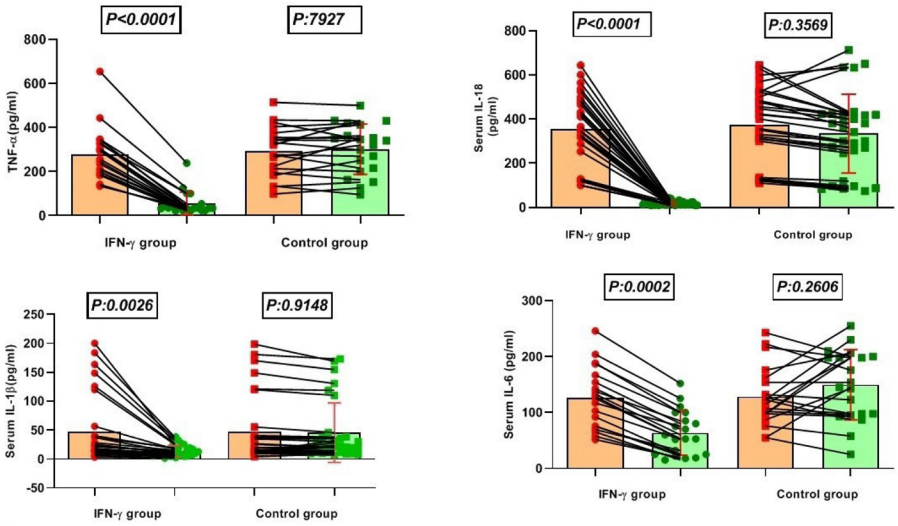

Figure 2. Outcomes Over Time.

outlines common signs, history of the disease, radiography findings, NEWS2, and SOFA assessment. Of 60 patients, 55 had lung involvement infection upon admission. The mean percentage was 50 (Min: 20, Max: 65) by both high-resolution CT and chest X-ray for both groups. The mean percentage of lung infection of the IFN-γ was 15% after 7 days of trial (CI: -38.97 to -28.03; $P<0.0001$). The control group lung infection had developed mild (ground-glass opacification, vascular dilatation, traction bronchiectasis) in 18 cases by 7 days and 3 had an intensive involvement lung infection (crazy paving expansion) with intubation and death outcome during 30 days' hospitalization, and the mean amount of infection achieved 60% (CI: -0.1109 to 14.24; $P=0.0535$). Ground-glass opacification was the most significant among all patients (80%). Crazy paving and Pleural effusion were observed within all 3 intubated patients.

NEWS2 score assessment performed every day upon admission and first day trial. The mean score on day 1 in both groups was [2 (1-4); $P=0.8042$, CI: -0.6025-0.4691]. The patients had been assessed by liver function and NEWS2 score 10 hours after the IFN-γ injection experiment. There was no side effect reported by patients and all claimed better general condition. The IFN-γ group achieved 0 scores of NEWS2 by 24 hours maintenance after 5 days upon trials and 3 doses of IFN-γ. Only one patient who had coronary artery history disease experienced 110 mm Hg systolic BP [0 (0-1)]. The control group had an irregular scoring pattern till day 7 compared with the IFN-γ group [1 (0-5); $P=0.0002$, CI: 0.5530-1.714].

Table 1. Hematology and Serology Results

Parameters	Interferon-γ-C Group					Control Group				
	Day1	Day 3	Day 7	*P* Value	F	Day1	Day3	Day7	*P* Value	F
WBC (4-10×10³ mm³)	4153	5343	6897	<0.0001	123.6	4147	4250	4250	0.4697	0.7624
Lymphocyte (%)	12.76	27.20	37.19	<0.0001	219.9	12.90	16.41	19.99	<0.0001	23.93
Neutrophil (%)	78.38	59.16	43.21	<0.0001	179.1	78.14	75.49	69.82	<0.0001	12.81
Platelet (15-45×10⁴ mm³)	151.8	191	273.8	<0.0001	79.56	151.5	155.4	161.2	0.4652	0.7720
ALP (42–110 U/L)	71.70	68.77	62.17	0.0076	5.160	71.80	61.63	48.53	<0.0001	51.02
CPK men (39-308 U/L)	517.5	418.4	278.8	<0.0001	51.47	555.1	513.1	455.2	0.0025	7.102
CPK women (26-192 U/L)	357.7	305.6	194.6	<0.0001	93.48	364.1	342.7	318.1	0.0874	2.575
CRP (IQR) (<1 mg/dL)	3	1	0	<0.0001	95.57	4	4	4	0.5713	0.5636
K⁺ (3.5-5.5 mmol/L)	3.716	4.058	4.333	0.0101	4.851	3.652	3.718	3.809	0.7384	0.3043
Na⁺ (135-145 mmol/L)	134.3	138	140.7	0.0009	7.642	136	137.8	138	0.6589	0.4191
LDH (235-470 IU/L)	576.9	431.3	315.9	<0.0001	68.22	575.9	549	490.8	0.0022	6.556
IL1B (0-5 pg/mL)	47.54	-	13.57	0.0026	-	46.98	-	45.45	0.9148	-
IL-6 (5-15 pg/mL)	129.8	-	51.73	<0.0001	-	127.3	-	137.3	0.4991	-
IL18 (pg/ml)	354	-	18.99	<0.0001	-	375	-	333.5	0.3569	-
TNF-α (0-16 pg/mL)	254.1	-	48.42	<0.0001	-	281.6		285.1	0.9028	-

*Serum Interleukins level were measured by enzyme linked immunosorbent assay (ELISA)

WBC, white blood cells; IL-1B, Interleukin 1B; LDH, lactate dehydrogenase; CRP, C-reactive protein; ALP, alkaline phosphatase.

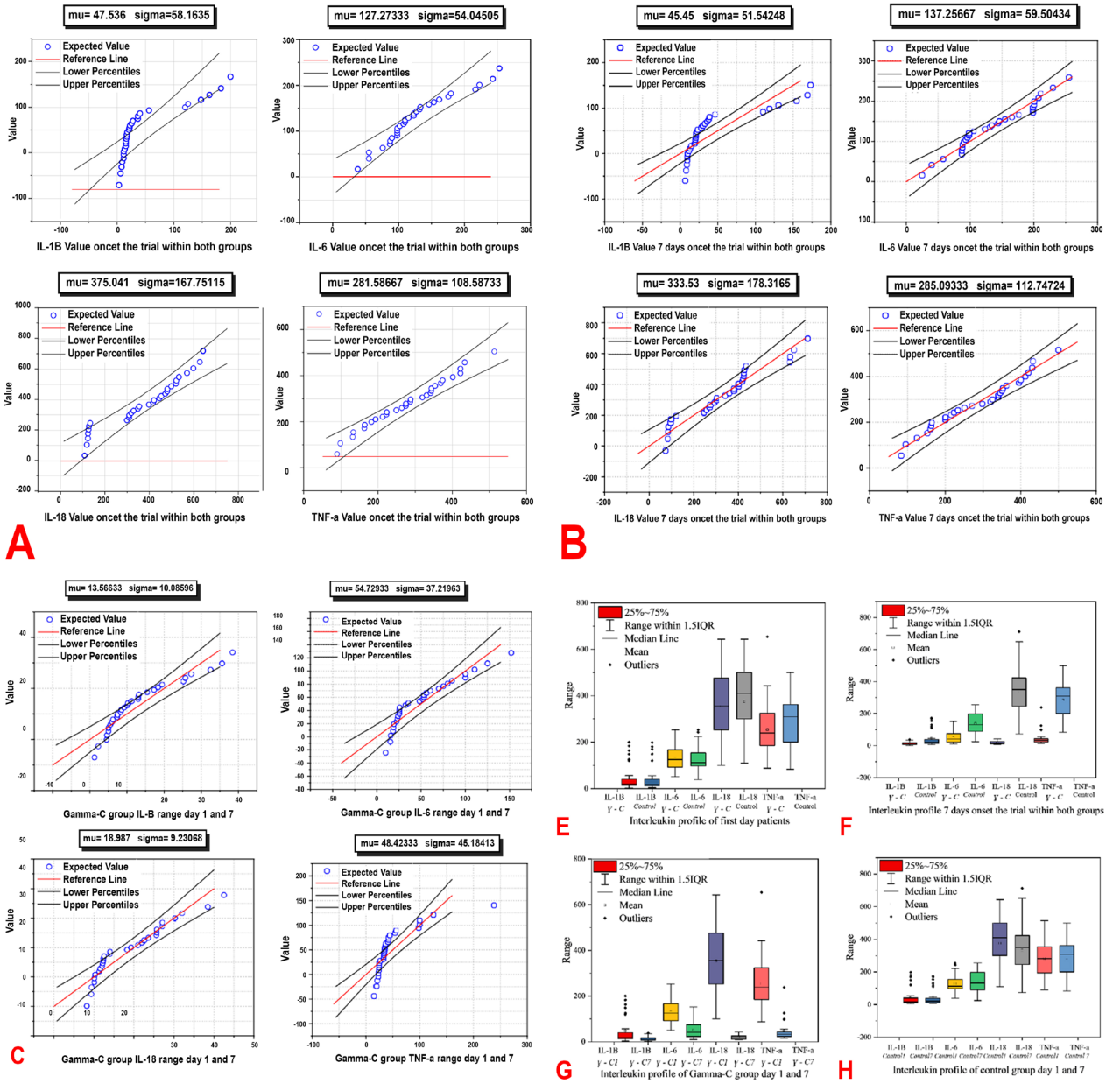

Figure 3. Outcomes over time; A, Interleukin profile 1 day onset the trial within both groups; B, Interleukin profile 7 days onset the trial within both groups; C, Interleukin profile of Gamma-C group day 1 and 7 after 3 doses injection; D, Interleukin profile of Control group day 1 and 7; E, Interleukin profile of Gamma-C group day 1 before 3 doses injection and control, Interleukin profile of Gamma-C group day 7 after 3 doses injection and control; G, Interleukin profile of Gamma-C group day 1 and 7 after 3 doses injection; H, Interleukin profile of Control group day 1 and 7.

Nevertheless, the Sequential Organ Failure Assessment (SOFA) Score had performed on days 1, 3, and 7 in both groups, and both had no significant difference in their mean score of the SOFA assessment on day 1 [1.16 and 1.20 (0-3) respectively, $P=0.8685$]. All IFN-γ treatment patients had better outcomes and achieved 0 scores of SOFA assessment [0 (0-0)], but 3 patients in the control group attained worse SOFA assessment by day 7 [0 (0-7); CI: 0.006245-1.594, $P=0.0483$].

The decision to perform real-time PCR to determine the SARS-CoV-2 negative test was made based on the normal results obtained from the hematological test and the patient's general condition based on NEWS2 and SOFA assessment. The IFN-γ treatment group had almost normal results in 5th day of the trial onset and their specimens were collected on day 7 from nasopharyngeal, oropharyngeal saliva, throat swab, and results reported by day after. All IFN-γ groups had negative RT-PCR results. The control group had a different pattern and the mean day of collecting specimens was 17 (12-25). The time to achieve a negative result was 18 (13-26) [CI: -11.59 to -8.517, $P<0.0001$]. The following describes complete statistical data.

Discussion

Our limited study might be the first application of the

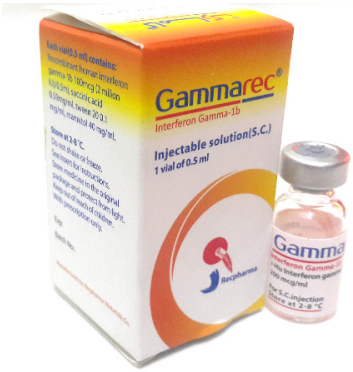

Figure 4. Recombinant human interferon gamma-1b 100 mcg (2 million IU)/0.5 mL (Manufacturer: Recpharma (Notarkib) Co.).

IFN-γ injection for curing cytokine storm caused by SARS-CoV-2. Affirmative results shall be achieved, and we encourage researchers and other medical centers to study extensively on IFN-γ. COVID-19 disease is joined by a forceful incendiary reaction with the arrival of a lot of supportive provocative cytokines in an occasion known as a "cytokine storm." The insusceptible reaction of the host to the SARS-CoV-2 infection is hyperactive leading to an over-the-top inflammatory response. A few examinations dissecting cytokine profiles from COVID-19 patients recommended that the cytokine storm corresponded legitimately with lung injury, multi-organ disappointment, and negative guess of serious COVID-19 (10-15).

The collected evidence implies that a few patients with serious COVID-19 experience the effects of a "cytokine storm." Analysis of cytokine levels in the plasma of 41 COVID-19-affirmed cases in China uncovered raised degrees of IL-1β, IL-7, IL-8, IL-9, IL-10, FGF, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1A, MIP1-B, PDGF, TNF-α, and VEGF in the two patients admitted to the ICU and non-ICU patients contrasted with grown-ups. All patients remembered for the investigation had pneumonia and 1/3 of the patients were admitted to ICU and six of these patients passed on (16). Also, Li et al, and many studies confirm that leukopenia, lymphocytopenia, and eosinophil cytopenia are more common in COVID-19 patients than those in non-COVID-19 patients (17). IFN-γ plays an important role in antiviral, anti-proliferative, immunomodulatory, and pro-inflammatory activities (18,19). IFN-γ is probably one of the most relevant cytokines orchestrating the immune response in vertebrates, and mammals (20). There is a study that showed the relationship between lymphopenia and high expression of IFN-γ (21). Thus, there might be a reasonable answer to the serous increased levels of lymphocytes after injectable anti-gamma interferon antibodies. Moreover, IFN γ is known to be a potent activator of macrophages which stimulates them to kill phagocytosed microbes and cancer cells and induces the production of TNF-α and interleukin-12 (22). Subsequently, it enhances platelet-derived growth factor subunit B (PDGF-B) (23) leading to raised platelets and compensate for platelet deficiency occurred SARS-CoV-2 disease as this study. IFN-γ, a cytokine with antiviral and immunomodulatory effects, has been effectively harnessed through recombinant DNA technology to enhance its therapeutic potential. The recombinant form of IFN-γ, produced through innovative genetic engineering techniques, demonstrates the ability to exert antiviral effects and modulate the immune response. IFN gamma-1b is utilized for its activity as a macrophage-animating component as an extra to antimicrobial treatment in constant granulomatous infection. It is likewise used to defer time to sickness supportive of regression and decrease the recurrence of genuine contaminations in patients with serious threatening osteoporosis (24), for the utilizing drug, see Figure 4.

For a brief description of the probabilistic-statistical analysis, this study used data considered normal. Data estimation was done based on input data such as Mu as the average of the normal distribution, and Sigma as the standard deviation of the normal distribution. Bloom's method had been selected to draw percentile approximations. In the normal distribution, the density function was:

$$\frac{1}{\sigma\sqrt{2\pi}}\exp\left(-\frac{(x-\mu)^2}{2\sigma^2}\right)$$

Mu, mean, is the location parameter and, sigma (>0), standard deviation, is the scale parameter. In Bloom score methods, input data is ordered from smallest to largest, and then the serial number of the sorted data is scored using the method listed above. In this method, i is the serial number and n is the total number of the non-missing input data $(i - 0.375)/(n + 0.25)$, based on the plotting position method (i,n) (25,26). All of this discussion is illustrated in Figure 5.

Conclusions

Immunological monitoring, adjunctive immunotherapy with IFN-γ appears well-tolerated with excellent outcomes in SARS-CoV-2 and probably is among the strongest anti-interleukin antibodies against cytokine storm and antiviral treatment. The findings of our research were quite convincing, and considering the summarized conclusions which is consistent with Figure 4, the virus absorbs into the epithelia through the ACE2 receptor. As more ACE2 receptors are occupied by viruses, angiotensin levels increase to compensate for the number of normal receptors on the endothelial surface. Such increase leads to the capillary permeability enhancing, consequently to the pulmonary edema. Apoptosis and tissue injury trigger the recruitment of various immune cells such as neutrophils, macrophages, plasmacytoid and dendritic cells to the site of injury. This process leads to the release of type 1 and 3 interferons, chemokines, alarmins, pro-inflammatory cytokines including IL-1B, IL-6, IL-18, IL-33, and TNF-α.

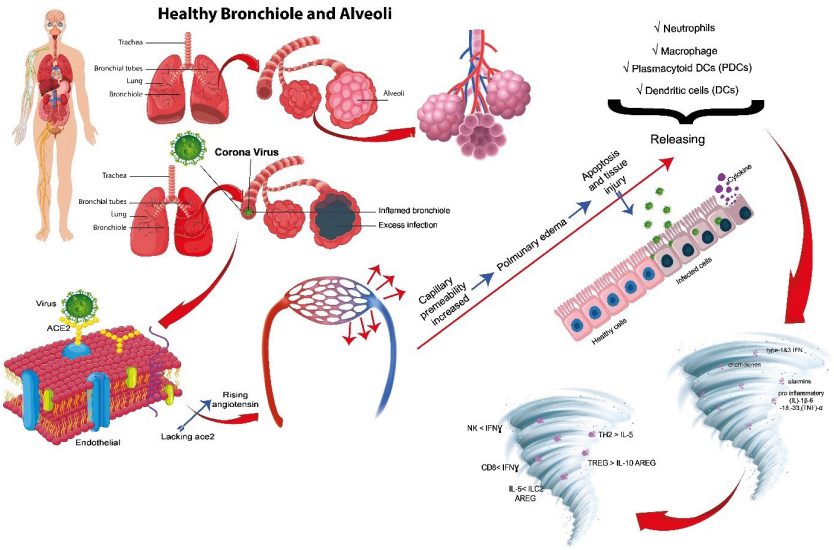

Figure 5. The modus operandi physiology of Cytokine storm caused by COVID-19.

Consequently, a secondary cytokine storm is formed involving TH2, TREG, NK cells, CD8 cells, and ILC2, resulting in the release of additional IL-5, IL-10, AREG, and IFN-γ. These events can ultimately contribute to the development of acute respiratory distress syndrome (27).

Authors' Contribution

Conceptualization: Sepideh Hassanpour Khodaei1and Leila Roshangar.
Data curation: Sepideh Hassanpour Khodaei.
Formal analysis: Majid Shokoohi, Negin Hadisi and Leila Roshangar.
Funding acquisition: Leila Roshangar.
Investigation: Majid Shokoohi, Negin Hadisi,Shahram Dabiri, Mehdi Gharekhani, Hanieh SalehiPourmeh, Shahla Meshgi.
Methodology: Negin Hadisi and Leila Roshangar.
Project administration: Leila Roshangar, Negin Hadisi.
Resources: Sepideh Hassanpour Khodaei, Shahla Meshgi.
Supervision: Leila Roshangar.
Validation: Negin Hadisi, Leila Roshangar and Majid Shokoohi.
Visualization: Sepideh Hassanpour Khodaei.
Writing-original draft: Majid Shokoohi, Negin Hadisi.
Writing-review & editing: Leila Roshangar, Sepideh Hassanpour Khodaei.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1399.130) and registered in the Iranian Registry of Clinical Trials website (identifier: IRCT20200525047570N1). All patients submitted written consent for participation in the study. IFN-γ expenses were disbursed by the Tabriz University of Medical Sciences.

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Supplementary files

Supplementary file 1 contains Table S1.

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