ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.2025.654
Asthma Allergy Immunol 2025;23:70-75

RESEARCH ARTICLE

Received: 26.08.2024 • Accepted: 14.01.2025
Online Published: 10.03.2025

Investigation of Adalimumab (CinnoRA) Effects in Controlling the Severe Form of COVID-19: A Randomized Controlled Trial

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ABSTRACT

Objective: Abnormal immune responses play a fundamental role in coronavirus disease 2019 (COVID-19). Overexpression of pro-inflammatory cytokines, especially tumor necrosis factor-alpha (TNF-α), is considered as one of the important factors in the development of the disease. Several monoclonal antibodies have been proposed to inhibit the function of TNF-α. Therefore, this study investigated the possible effects of a biosimilar Adalimumab named CinnoRA ®, a TNF-α inhibitor, on patients with severe COVID-19.

Materials and Methods: This randomized clinical trial was conducted on 80 patients infected with severe COVID-19. After confirming the disease, patients were selected with simple random sampling and divided into two groups, including patients receiving subcutaneous injections of 80 mg of adalimumab and standard treatments (case group) and those only treated with standard treatments (control group). The demographic features, clinical symptoms, laboratory findings, and other information were recorded during hospitalization.

Results: No patients in the case group required ventilatory support and only one case died due to COVID-19, whereas three cases of the control group needed ventilatory support and died during hospitalization. Although there were differences in the values of peripheral blood oxygen saturation (SpO2), erythrocyte sediment rate (ESR), C-reactive protein (CRP), and hospitalization duration between subjects treated with and without adalimumab, these alterations were not statistically significant.

Conclusion: The treatment with adalimumab failed to exert significant changes in clinical and laboratory parameters participating in the recovery and outcome of COVID-19.

Keywords: Adalimumab (CinnoRA), COVID-19, tumor necrosis factor-alpha (TNF-α), immune responses

INTRODUCTION

Coronavirus disease 2019 (COVID-19), as a highly infectious disorder, causes a broad spectrum of clinical manifestations, ranging from asymptomatic cases or mild symptoms (cough, fever, myalgia, and weakness) to severe pneumonia leading to systemic inflammation and acute respiratory distress syndrome (ARDS) (1-4). Although the exact mechanism of ARDS in the mortality of COVID-19 patients is not fully understood, previous studies have pointed out that excessive production of pro-inflammatory cytokines (cytokine storm) plays a pivotal role in this field (3,5-7).

Numerous studies have shown the elevated production of inflammatory mediators such as MIP-1A, MCP-1, IP-10, tumor necrosis factor-alpha (TNF-α), PDGF, MIP-1B, IL-6, and VEGF in severe COVID-19 patients compared to healthy subjects (8-12). Others have revealed that severe COVID-19 patients who required intensive care unit

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(ICU) therapy showed enhanced values of pro-inflammatory cytokines, including IL-1, IL-8, INF-γ, GM-CSF, and G-CSF (5,13). Therefore, in addition to antiviral therapies, anti-inflammatory treatments can be helpful in the reduction of clinical manifestations and mortality in COVID-19 patients (5).

TNF-α is considered an important cytokine in the cytokine storm that contributes to initiating inflammatory responses, exacerbating inflammation, and producing other pro-inflammatory cytokines (5). TNF-α has two receptors including TNFR1 and TNFR2 that are expressed on a variety of cells and peripheral tissues. TNFR1 acts as the main receptor that is activated by binding to soluble and membrane-bound active forms of TNF-α and is responsible for initiating inflammatory responses and mediating apoptosis (14,15). TNFR2 is activated by the membrane-bound form and expressed in specific cell types, such as oligodendrocytes, microglia, astrocytes, endothelial cells, lymphocytes, and cardiac myocytes (16,17). This receptor facilitates antiviral immune responses by stimulating the production of cytotoxic T lymphocytes (18).

Several monoclonal antibodies have been proposed to inhibit the function of TNF-α, including golimumab, infliximab, adalimumab, certolizumab, and etanercept (9). These inhibitors have been used for many years in severe inflammatory autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, and ankylosing spondylitis (19).

Adalimumab is a two-armed IgG1 monoclonal antibody that binds to TNF-α and neutralizes its biological function by preventing its interaction with TNFR1 and TNFR2 receptors. A biosimilar form of adalimumab is available in Iran under the generic name of CinnoRA, which is usually used for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriasis, and psoriatic arthritis (9).

Previous studies have mentioned that TNF-α inhibitors may be effective in patients with severe COVID-19 (19-21). Others have reported that adalimumab, as an adjuvant drug, is able to improve blood oxygen levels and decrease serum CRP and lactate dehydrogenase levels in patients with severe COVID-19 (22).

Given that previous studies have pointed to TNF-α inhibitors exerting valuable therapeutic impacts in controlling and managing COVID-19, the present study aimed to investigate the potential therapeutic effects of adalimumab in treating COVID-19 cases in combination with standard treatments.

MATERIALS and METHODS

In the present randomized clinical trial, 80 patients with severe COVID-19 were recruited among individuals referred to the infectious diseases ward of Shahid Beheshti Hospital, Kashan, Iran from April 2021 to November 2021. The COVID-19 diagnosis and its severity were confirmed by an infectious diseases specialist based on clinical and laboratory criteria, including fever, fatigue, cough, headache, myalgias, dyspnea, diarrhea, peripheral blood oxygen saturation (SpO_2), CRP, ESR, complete blood count (CBC), SARS-CoV-2 RNA detection in respiratory secretions, and chest radiography. According to the instructions on the treatment and management of COVID-19, severe patients had dyspnea, an SpO_2 of ≤ 93% on room air, a respiratory rate of 30 or more breaths per minute, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FiO_2) of < 300 mm Hg, or infiltrates in more than 50% of the lung field (1,5). Some patients needed mechanical ventilation. Pulmonary involvement was determined using Chest CT scan imaging as described by previous studies (13). At the time of admission, nasopharyngeal swab samples were collected from all participants and real time-polymerase chain reaction (RT-PCR) assay was carried out to determine the SARS-CoV-2 RNA. None of the patients were on treatment with immunosuppressive drugs before entering the study. All patients suffered from clinical features of COVID-19 at least 3–5 days prior to being referred to Shahid Beheshti Hospital to initiate disease treatments. Exclusion criteria included: 1) patients with other infectious disorders, autoimmunity, malignancy, and other diseases affecting the immune system; 2) subjects on treatment with immunosuppressive drugs.

The study was approved by the Ethics Committee of Kashan University of Medical Sciences (IR.KAUMS.REC.1400.049) and the trial was registered as IRCT20180209038673N6. A written informed consent was obtained from all patients and the legally authorized representatives of dead cases prior to study initiation.

Study Design

The patients were randomized according to a permuted block randomization scheme. Patients were categorized into case and control groups. In the case group, 40 patients received adalimumab (CinnoRA®, CinnaGen, Iran), 80 mg, single-dose, subcutaneously in prefilled syringe form.

The 40 subjects in the control group were not treated with adalimumab. Before treatment with adalimumab, purified protein derivative (PPD) skin test and chest X-rays were employed to determine tuberculosis infection. Two groups received standard treatments, including oxygen and fluid support, remdesivir (200 mg on day 1 followed by 100 mg on days 2–8 in single daily infusions), dexamethasone (8 mg intravenously daily for eight days or up to the point of discharge), ceftriaxone (1 gr twice/day for eight days or up to the point of discharge), and heparin therapy (50 mg, single-dose, subcutaneously in prefilled syringe form).

Disease Outcomes

Data collection was performed using the medical records of patients regarding gender, age, underlying diseases, results of laboratory tests, and SpO_2. The outcomes of the disease were divided into two groups. The primary outcomes included the necessity of mechanical ventilation, home oxygen therapy, and the mortality rate. These outcomes were investigated until death or discharge from the hospital. The secondary outcomes were disease duration, dyspnea and cough duration, fever duration, and SpO_2, ESR, and CRP values. Clinical features and SpO_2 were recorded daily during the hospitalization period. Laboratory parameters were measured on the first, second, and third days and before discharge from the hospital.

Statistical Analysis

The results were analyzed using GraphPad Prism 6 (GraphPad Software, USA) and are represented as the mean ± standard deviation (SD). The Kolmogorov–Smirnov test was employed to determine the normal distribution of data. According to non-normal distribution of data, the Mann–Whitney test was used to compare two groups. The correlations were studied using the Fisher's exact and Chi-square tests. p values less than or equal to 0.05 were considered statistically significant.

RESULTS

A total of 80 patients with severe COVID-19 (34 males and 46 females, aged 23 to 93 years) were enrolled in the study. The mean age ± SD of the patients was 56.56±16.92. Of the 40 patients who received adalimumab, 22 (55%) had no comorbidities, while this number was 13 (32.5%) in the control group. There was no statistically significant relationship in age, gender, comorbidity rates, diabetes, high blood pressure, obesity, heart disease, and other clinical findings between the case and control groups (Table I). No significant difference was observed in disease duration between those treated with and without adalimumab. The demographic and other information of severe COVID-19 individuals are indicated in Table I.

The Primary Outcomes

Regarding the necessity of mechanical ventilation and rate of mortality, none of the patients who received adalimumab needed mechanical ventilation and died due to COVID-19, while three cases who did not receive adalimumab required mechanical ventilation and died during treatment. In the case group, 20 cases (50%) required home oxygen therapy, while it was 18 (45%) in the control group. Although there were differences between the groups in terms of primary outcomes, these alterations were not statistically significant.

Table I: The demographic and clinical characteristics of patients with severe COVID-19.

Variable	Control group (n=40)	Case group (n=40)	p value
Age (year, mean ±SD)	59.1±16	54.1±17.6	0.19
Gender (male), n (%)	19 (47.5)	15 (37.5)	0.498
Number of comorbidities, n (%)	27 (67.5)	18 (45)	0.220
Background diseases, n (%)	Diabetes: 18 (45) Hypertension: 15 (37.5) Obesity: 7 (17.5) IHD: 8 (20)	Diabetes: 9 (22.5) Hypertension: 16 (40) Obesity: 4 (10) IHD: 6 (15)	NS
Disease duration, (day, mean±SD)	6.1±3.3	5.5±3.1	0.366
Temperature (°C)	37.7±0.5	37.6±0.5	0.624
Respiratory rate	19.1±1.8	19.9±6.8	0.45

IHD: Ischemic heart disease. The Fisher's exact and Chi-square tests were employed to analyze the correlations, while the Mann–Whitney test was used to compare data with non-normal distribution.

The Secondary Outcomes

To determine the effects of adalimumab on clinical and laboratory findings of COVID-19, the values of SpO_2 were measured on the first, second, and third days of the hospitalization, and discharge time of the patients. In patients who received adalimumab, the mean SpO_2 on the first day of the hospitalization was 89.7%, which reached 94% at discharge time. In the control group, it was respectively 89.8% and 93.6% on the first day of the hospitalization and at discharge time (Table II). There was no statistical difference in the values of the SpO_2 between the case and control groups (Table III).

In the next step, the effects of adalimumab on laboratory parameters related to COVID-19 were studied. Our data revealed that the mean of ESR in the case group was 40.8 mm/hour on the first day of the hospitalization and 22.5 mm/hour on the third day of the hospitalization. In the control group, the mean ESR level was 39.3 mm/hour on the first day of the hospitalization, which decreased to 27.2 mm/hour on the third day of the hospitalization. After removing the time effect, there was no significant difference in ESR changes between the case and control groups.

Other results indicated that the mean CRP value in the case group was 73.5 mg/L on the first day of the hospitalization, which decreased to 27.1 mg/L on the third day of the hospitalization. In the control group, the mean of CRP was 68.4 mg/L on the first day of the hospitalization, which decreased to 27.5 mg/L on the third day of the hospitalization. After removing the time effect, there was no significant difference in CRP change between the case and control groups.

A significant difference was observed in cough duration between the case and control groups ($p = 0.012$). However, there was no significant difference in fever duration and dyspnea duration between those treated with and without adalimumab (Table III).

Table II: The values of SpO_2 in participants during the disease.

	Control group (n=40)	Case group (n=40)	p value
The first day	89.8±2.7	89.7±4.4	0.715
The second day	91±2.7	91.2±3.7	
The third day	92.6±1.9	93.1±3.2	
Discharging time	93.6±2.4	94±2.5	

The results were compared using the Mann–Whitney test and are shown as mean±SD.

DISCUSSION

There are some studies indicating that a single dose of anti-TNFα antibody can significantly reduce the amount of TNF-α in the blood (10), suggesting a possible anti-inflammatory benefit of adalimumab for COVID-19 (9). Previous studies have revealed that patients who had rheumatologic disorders and were on treatment with TNF-α inhibitors usually suffered from a mild form of COVID-19 compared to healthy subjects (8,12). Therefore, the current study was focused on determining the impacts of adalimumab in controlling severe forms of COVID-19.

There is significant inconsistency in the literature regarding the impacts of adalimumab on COVID-19 outcomes. Some reports have shown that adalimumab did

Table III: The secondary outcomes of severe COVID-19 in participants

Parameters	Control group (n=40)	Case group (n=40)	p value
The necessity of mechanical ventilation	3 (7.5)	0 (0.0)	0. 241
Mortality rate	3 (7.5)	0 (0.0)	0. 241
Home oxygen therapy	18 (45)	20 (50)	0.823
SpO_2>92	32 (80)	36 (90)	0.348
Side effects	1 (2.5)	0 (0.0)	-
Dyspnea duration (day)	4.2±2.7	3.8±1.7	0.456
Cough duration (day)	6.9±3.3	5.2±2.5	0.012
Fever duration (day)	2±2.1	2.5±1.7	0.238

Data are shown as mean±SD and percent (%). The Fisher's exact and Chi-square tests were employed to analyze the correlations, while the Mann–Whitney test was used to compare data with non-normal distribution.

not have significant effects on the rate of mortality and the need for mechanical ventilation (9). In agreement with this finding, the results of the current study revealed that none of the patients treated with adalimumab needed mechanical ventilation and died due to COVID-19, while three cases of the control group required mechanical ventilation and died during treatment. Other results indicated that there is no significant difference in the need for home oxygen therapy between the case and control groups. However, there are some studies revealing treatment with TNF inhibitors in patients with COVID-19 exerts a protective effect on the need for hospitalization and ICU therapy (23). It is shown that patients on treatment with anti-TNF therapy had a reduction in the rate of COVID-19 poor outcomes and death compared to those on alternative agents (11). Furthermore, TNF inhibitors were found to be inversely correlated with the composite outcome of death or hospital admission for COVID-19. However, treatment with anti-TNF did not affect the need for ICU therapy, or mechanical ventilation (24). This discrepancy could be attributed to the type of anti-TNF therapy and patients used in these studies. The effects of TNF inhibitors on COVID-19 outcomes are mainly reported by the studies on patients with autoimmune disease, who were on various types of anti-TNF inhibitors, including golimumab, infliximab, adalimumab, certolizumab, and vedolizumab, and who developed COVID-19 (23,25). Therefore, delay in treatment may limit the effectiveness of anti-TNF therapy (9).

In the next step, the impacts of adalimumab on clinical and laboratory findings of severe COVID-19 patients were studied. Our data indicated that adalimumab failed to influence SpO_2 values during treatment. Previous studies have shown that a three-day treatment with adalimumab exerts a negative impact on CRP levels in patients with COVID-19, which may relate to its anti-inflammatory effects (9). However, the current study revealed that the values of ESR and CRP in patients who received adalimumab did not significantly differ from those treated with other alternative agents. No difference in ESR and CRP values between case and control groups may contribute to the anti-inflammatory effects of treatment used on patients. In line with the effects of adalimumab on clinical characteristics, a significant difference was observed in cough duration between patients treated with adalimumab and those who received other immunosuppressive agents. However, this significant difference was not observed in fever duration and dyspnea duration between those treated with and without adalimumab. Although there are some studies pointing to no effects of adalimumab on clinical features of severe cases of COVID-19 (9), several reports have pointed to suppressive effects of adalimumab and infliximab on pathological inflammatory signals of COVID-19 and supportive impacts on the recovery disease (26). This inconsistency may relate to disease severity of patients, confounding effects of combination therapy with an immunomodulatory, and dose-dependent impact of TNF inhibitor used in different studies.

CONCLUSION

Although some studies are showing anti-inflammatory benefits of adalimumab in combination with other therapeutic agents in patients with autoimmune disorders who are infected with SARS-CoV 2, our data failed to reveal therapeutic benefits for adalimumab in combination with standard treatments in severe COVID-19 cases. A limitation of the study was no measurement of TNF-α levels in patients before treatment initiation. It seems that the lack of efficiency of anti-TNF-α therapy may correlate to the decreased level of TNF-α, which is observed in some severe cases of COVID-19.

Acknowledgments

The authors would like to thank all subjects who participated in the study and the Clinical Research Development Unit of Kashan Shahid Beheshti Hospital for its help.

Finding

This work was supported by grants from the Deputy of Research, Kashan University of Medical Sciences (Grant No: 400121).

Declaration of Interest

The authors declare no conflict of interest.

Consent to Participate

Informed consent was taken before taking part in the study.

Consent for Publication

All authors agree to publish the article.

Data Availability Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

Authorship Contributions

Concept: **Batool Zamani,** Design: **Khadije Ghavamnezhad,** Data collection or processing: **Morteza Sheikhi,** Analysis or Interpretation: **Hossein Akbari,** Literature search: **Batool Zamani,** Writing: **Hossein Motedayyen,** Approval: **Ahmad Najafi.**

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