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ORIGINAL ARTICLE

Report of Cases of COVID-19 in Patients Receiving Adalimumab Referred to the Rheumatology Clinics in Ahvaz City, Iran: Retrospective Cohort Study

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KEYWORDS

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ABSTRACT: This hypothesis has been proposed that the use of adalimumab in patients can prevent the damage caused by the cytokine storm in the patient's body. However, so far, there is not enough evidence regarding the role of the spread of COVID-19 in patients receiving adalimumab. In a cross-sectional study, 102 rheumatic patients sent to the rheumatology department for further assessment (Imam Khomeini and Golestan hospitals in Ahvaz from March 2018 until March 2021) who had taken adalimumab in the last six months to one year and were infected with COVID-19 were admitted. In this study, participants were assigned to two groups: the control group comprised rheumatic persons who did not receive adalimumab but had COVID-19, while the case group consisted of rheumatic patients with COVID-19 who were treated with adalimumab. The average age in the control and adalimumab groups was 43.11±6.43 and 39.90±11.08 years, respectively [P=0.09]. The duration of illness in the control and adalimumab groups was 7.8±6.69 and 6.45±4.56 years, respectively [P=0.08]. Positive PCR results were found in 47.1% of patients in the control and 52.9% in the adalimumab group [P=0.346]. CT scan results showed that 21.6% of patients in the control group and 29.4% in the adalimumab group exhibited pulmonary involvement, there was a statistically significant difference between the two groups. The length of hospitalization in the control and adalimumab groups was 3.07±1.27 and 2.9±1.3 days, respectively [P=0.976]. The difference in mortality between the two groups was not statistically significant [P=0.75]. Overall, these findings suggest that the use of adalimumab did not have an impact on the clinical improvement of patients with COVID-19.

INTRODUCTION

On December 31, 2019, the first case of a patient with pneumonia who was infected with a virus from the coronavirus family was reported in China, and this virus was known as SARS-COV-2[1-3]. After infection, this virus causes inflammatory reactions due to the occurrence of cytokine storm in patients[4]. Rheumatic patients who take immunosuppressive drugs are associated with an elevated risk of developing this

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disease. Therefore, these patients need special conditions to prevent infection [5, 6].

So far, no evidence has been shown that the incidence of corona in rheumatic patients is higher compared to the population [7, 8]. It has been shown that the use of some drugs as well as insights into the pathogenesis of rheumatic diseases could contribute to predicting the survival rates of rheumatic patients with COVID-19 [9]. The use of drugs or rheumatic disease has not been determined on susceptibility to infection and increased mortality of rheumatic cases [9, 10].

On the other hand, it has been reported that due to the fact that the occurrence of a cytokine storm causes an elevation in inflammatory cytokine production and a greater reliance on drugs that target them can prevent the deterioration of tissue damage caused by COVID-19 in rheumatic patients [4, 11].

In rheumatic patients, due to the autoimmune responses that occur and the activation of the immune system against the body's tissues, the levels of these cytokines increase [12]. Adalimumab is a monoclonal antibody directed against the cytokine TNF-α. This drug is commonly used in rheumatic patients to prevent the activation of immune system cells and the occurrence of inflammatory reactions against the joints and tissues of the body. Recent studies have shown that the incidence of clinical severity was reduced in rheumatologic patients receiving adalimumab [12-14]. In the introduction, the main hypothesis, which is "the use of Adalimumab may reduce the clinical symptoms of COVID-19," is not explicitly stated. It would be helpful if this hypothesis were clearly presented at the end of the introduction so that readers can fully grasp the study's objective.

The objective of this research was to evaluate the influence of adalimumab on both the prevalence and severity of COVID-19 symptoms in rheumatic disease patients.

MATERIALS AND METHODS

Within this cross-sectional investigation, rheumatic cases who were directed to the rheumatology clinics of Imam Khomeini and Golestan hospitals in Ahvaz between March 2018 and March 2021, and who had received adalimumab within the last six months to one year, were included if they were also diagnosed with COVID-19. Patients with incomplete medical records were excluded from the study. COVID-19 diagnosis was confirmed by the attending physician based on clinical examination and para-clinical findings. The participants were divided into two groups: the control group, which consisted of rheumatic patients who had COVID-19 but had not received adalimumab, and the case group, which included rheumatic patients with COVID-19 who had been treated with adalimumab. Data regarding hospitalization duration, severity of lung involvement, and mortality rate were collected using a questionnaire. The two groups were then compared based on demographic characteristics, clinical symptoms, and the severity of COVID-19.

Inclusion criteria

Rheumatic patients referred to the rheumatology clinics of Imam Khomeini and Golestan hospitals in Ahvaz between March 2018 and March 2021. Patients who had been taking adalimumab in the last 6 months to 1 year.

Patients diagnosed with COVID-19, with confirmation of infection based on clinical assessment and relevant paraclinical results.

Exclusion criteria

Patients with incomplete medical records.

Confirmation of COVID-19 infection

The diagnosis of corona in cases was confirmed by the treating physician based on paraclinical tests. These tests included the following:

RT-PCR (Reverse Transcription Polymerase Chain Reaction) was the key diagnostic test for COVID. Nasopharyngeal swabs and other respiratory samples were collected from patients and tested for the presence of SARS-CoV-2 RNA. This technique is regarded as the gold standard for confirming a COVID-19 diagnosis.

CT Scan (Computed Tomography)

In addition to RT-PCR, chest CT scans were performed to evaluate the extent of lung involvement in patients with respiratory symptoms or severe COVID-19. CT scans can identify common features of COVID-19-

related pneumonia, such as ground-glass opacities, and provide useful information regarding the severity of lung damage.

In certain cases, rapid antigen tests or serology tests were used as supplementary diagnostic tools to confirm COVID-19 infection; however, these were not the primary methods employed in this study.

Statistical analysis

The data were processed and analyzed using the Statistical Package for the Social Sciences (SPSS), version 22 (IBM, Chicago, USA). For continuous variables, descriptive statistics were expressed as the mean ± standard deviation (SD), while categorical variables were represented as frequencies and percentages. The normality of the data was examined using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Group comparisons were conducted using either the T-test or the Mann-Whitney U test, depending on the distribution of the data. For categorical variables, differences between groups were analyzed using either the Chi-square test or Fisher's exact test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The mean age of participants in the control and adalimumab groups was 43.11 ± 6.43 years and 39.90 ± 11.08 years, respectively, with no statistically significant age difference between the groups (P = 0.09). The duration of the disease in the control group was 7.8 ± 6.69 years, while in the adalimumab group it was 6.45 ± 4.56 years (P = 0.08). The proportion of females was 62.7% in the control group and 58.8% in the adalimumab group (P = 0.421). No significant differences were observed in the types of rheumatic diseases between the two groups (P = 0.147). Further details can be found in Table 1.

Table 1. Demographic and clinical information of patients in two control and intervention groups.

Variable		Control group [n=51]	Adalimumab group [n=51]	P-value
Age [Year], mean±SD		43.11±6.43	39.90±11.08	0.09
Duration of disease [year], mean±SD		7.8±6.69	6.45±4.56	0.08
Sex, n [%]	**Female**	32 [62.7]	30 [58.8]	0.421
	Male	19 [37.3]	21 [41.2]	
Type of disease, n [%]	**Rheumatoid arthritis**	33 [64.7]	23 [45.1]	0.147
	Ankylosing spondylitis	15 [29.4]	19 [37.3]	
	Psoriatic arthritis	2 [3.9]	7 [13.7]	
	Juvenile rheumatoid arthritis	1 [2.0]	2 [3.9]	

The mean duration of treatment with adalimumab was 19.5 ± 11.8 months. In the control group, 47.1% of patients tested positive for PCR, compared to 52.9% in the adalimumab group (P = 0.346). According to CT scan findings, 21.6% of individuals in the control group and 29.4% in the adalimumab group exhibited pulmonary involvement, with a significant difference between the two groups (P = 0.01). The hospitalization rate was 82.4% for the control group and 80.4% for theadalimumab group (P = 0.5). While hospitalization rates were similar, the number of patients admitted to the ward was slightly higher in the control group, although this difference was not statistically significant (P = 0.88). No significant difference in mortality rates was observed between the two groups (P = 0.75). The average length of hospitalization was 3.07 ± 1.27 days in the control group and 2.9 ± 1.3 days in the adalimumab group (P = 0.976), as detailed in Table 2.

Table 2. Disease severity of COVID-19 in two control and intervention groups of rheumatic patients.

.Variable		Control group [n=51]	Adalimumab group[n=51]	P-value
Duration of treatment with adalimumab [months], mean±SD		0	19.5±11.8	0.0001
Positive PCR, n [%]		24 [47.1]	27 [52.9]	0.346
CT SCAN, n[%]	**No CT SCAN**	39 [76.5]	27 [52.9]	0.01
	with lung involvement	11 [21.6]	15 [29.4]	
	Without lung involvement	1 [2.0]	15 [29.4]	
hospitalization, n[%]		42 [82.4]	41 [80.4]	0. 5
Type of treatment of COVID-19, n[%]		27 [52.9]	24 [47.1]	0.88
		15 [29.4]	17 [33.3]	
		8 [15.7]	8 [15.7]	
Life status , n[%]	**Alive**	50 [98]	50 [98]	0.75
	Dead	1 [2]	1 [2]	
Duration of hospitalization, days [mean±SD]		3.07±1.27	2.9±1.3	0.976

DISCUSSION

Several investigations have assessed the potential therapeutic effects of adalimumab in managing COVID-19. Available evidence suggests that patients with rheumatic conditions who are treated with TNF-α inhibitors, such as adalimumab, tend to experience less severe disease progression compared to those not receiving these medications [41]. Fakharian et al. found that adalimumab treatment was linked to a reduction of less than 35% in the need for mechanical ventilation, although ICU admissions did not significantly differ between the adalimumab and control groups [15]. These findings are consistent with the results of the present study, which showed that the ICU admission rate was identical (15.7%) in both the adalimumab and control groups (P = 0.88).

In our analysis, we observed a higher number of positive PCR and CT scan results in the adalimumab group compared to the control group. However, no statistically significant differences were found between the groups (P > 0.05). These findings are in line with those reported by Fakharian et al., particularly regarding the CT scan results.

Fakharian et al. also reported similar mortality rates between the adalimumab-treated and control groups, which aligns with the results of our study. Furthermore, their study indicated a lower hospitalization rate in the adalimumab group and a reduction in pulmonary involvement. However, in contrast, our study found a higher rate of pulmonary involvement in the adalimumab group compared to the control group, which differs from Fakharian et al.'s results. This inconsistency may be attributed to variations in sample size and study design.

Fakharian et al. also noted a significant reduction in CRP levels in the adalimumab group after 3 days, suggesting an anti-inflammatory effect of adalimumab in this context. Given the inflammatory nature of COVID-19 in the lungs, it is plausible that TNF-α levels in the lungs may be higher than those in the bloodstream, which could explain the reduction in CRP levels observed after 3 days of adalimumab treatment. White blood cell count and TNF-α levels also decreased after 3 days, but this change was not statistically significant [15]. In contrast, our study did not compare CRP and TNF-α levels between the two groups.

Another study indicated that long-term adalimumab treatment in patients with inflammatory bowel diseases led to less severe COVID-19 and reduced pulmonary involvement [15]. This finding is inconsistent with our results, which may be explained by differences in sample size and the type of diseases being investigated. While the aforementioned study focused on patients with inflammatory bowel disease, our study examined individuals with rheumatic diseases.

In the study by Fredi et al., the prevalence of COVID-19 in both adalimumab-treated and other immunosuppressive drug-treated groups was similar, with no significant differences in mortality rate or the severity of clinical symptoms between the groups [16].

These findings align with the results of our study.

Similarly, the research conducted by Haberman et al. found no significant association between hospitalization rates and the use of various treatments, including adalimumab, corticosteroids, and IL-6 inhibitors [17]. In the present study, no significant difference in hospitalization rates was observed between the adalimumab and control groups. These findings are consistent with those of Dalifer et al., who also reported no significant differences in hospitalization rates between the two groups.

In the study of Haberman et al, the results showed that rheumatic patients with COVID-19 who received adalimumab had milder clinical symptoms and less pulmonary involvement compared to patients who received corticosteroids[17]. The findings of this study are inconsistent with our results. Contrary to the findings of our study, Akiyama et al. reported that patients receiving corticosteroids had a significantly worse clinical condition and higher mortality compared to patients receiving Adalimumab[18]. The difference in sample size and different study designs of the two studies may be the cause of this discrepancy.

COVID-19, as a novel viral disease, has had profound impacts on global health, leading to significant challenges in healthcare systems. In addition to its direct effects, the pandemic has exacerbated and triggered various chronic and rheumatic diseases, respiratory issues, and immune disorders in patients, creating new challenges in their treatment and management [19-26].

Study limitations

The limitations of the study include the exclusion of patients with incomplete medical histories, which may introduce bias in the results, the short follow-up period that does not account for the long-term effects of COVID-19, and the possibility of overlooking mild or asymptomatic cases of COVID-19.

CONCLUSIONS

The use of adalimumab did not show a significant effect on the improvement of clinical symptoms in patients with COVID-19. One possible explanation for this lack of impact is that elevated levels of TNF-α might be a more reliable indicator of the potential effectiveness of anti-TNF-α therapy. Furthermore, the relatively small sample size in this study may have contributed to the lack of observed therapeutic benefits, suggesting that larger studies with more participants are needed to reach more definitive conclusions. Additionally, the retrospective nature of the study, which relied on existing clinical data, may limit the generalizability of the findings. A clinical trial design could have yielded more robust results. Another limitation was the absence of a comparison of laboratory parameters, particularly the levels of TNF-α and other inflammatory markers between the two groups. Future clinical trials with larger sample sizes are recommended to further validate these findings.

CONFLICT OF INTERESTS

None.

ETHICAL CONSIDERATION

The current study was performed based on Helsinki declarations and was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran with Ethical Code: IR.AJUMS.REC.1400.533. The local institutional ethics committee of study center oversaw the proceedings and documentation.

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