Acta Medica Alanya

RESEARCH ARTICLE

ARAŞTIRMA

Acta Medica Alanya

2024;8(1): 43-48

DOI: 10.30565/medalanya.1443962

Effect of Tocilizumab Treatment on Seroconversion in Hyperinflammation Secondary to Covid 19

Covid 19'a Bağlı Hiperinflamasyonda Tocilizumab Tedavisinin Serokonversiyon Üzerine Etkisi

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ABSTRACT

Aim: During the ongoing COVID-19 pandemic, the management of hyperinflammation, a serious symptom that occurs secondary to the disease, has emerged as a major challenge. Tocilizumab, an immunosuppressive drug, offers a potential solution. However, it is extremely important to understand its effects on antibody formation after recovery from Covid-19. Therefore, our study aimed to investigate the effects of tocilizumab treatment on antibody production by measuring SARS-COV-2 spike total antibody levels at the third month post-infection in patients receiving this specific treatment.
Materyal and Methods: Our study incorporated 48 patients diagnosed with Covid 19 who presented with hyperinflammation during hospitalization. These patients, admitted to our institution, were treated with tocilizumab and subsequently discharged. We meticulously determined the 3rd month SARS-COV-2 spike total antibody levels in these patients.
Results: The participants of the study, characterized by a mean age of 52.5 ± 11.6 years, demonstrated positive SARS-COV-2 spike total antibody levels at 3 months, irrespective of age, gender, comorbidity, and length of hospital stay. The mean antibody levels in the patient population were quantified to be 223.58 ± 68.36 U/mL, with a range from 14.2 to 250 U/mL.
Conclusion: Our findings reveal that all patients exhibited positive antibody levels at 3 months following tocilizumab treatment.This suggests that the administration of tocilizumab in the management of hyperinflammation secondary to Covid 19 does not adversely affect antibody formation, at least in the short term. This could have substantial implications for future treatment strategies.

Keywords: Covid 19; IL-6; Hyperinflammation; Tocilizumab; Antibody

ÖZ

Amaç: Devam eden COVID-19 pandemisi sürecinde, hastalığa ikincil olarak ortaya çıkan ciddi bir semptom olan hiperinflamasyonun yönetimi büyük bir meydan okuma olarak karşımıza çıkmıştır. İmmünsüpresif bir ilaç olan Tocilizumab, potansiyel bir çözüm sunmaktadır. Ancak, Covid-19'dan iyileşme sonrası antikor oluşumu üzerindeki etkilerini anlamak son derece önemlidir. Bu nedenle, çalışmamız bu spesifik tedaviyi alan hastalarda, enfeksiyon sonrası üçüncü ayda SARS-COV-2 spike toplam antikor seviyelerini ölçerek, tocilizumab tedavisinin antikor üretimi üzerindeki etkilerini araştırmayı amaçlamıştır.
Yöntemler: Çalışmamız, hastaneye yatırıldıkları sırada hiperinflamasyon gösteren ve Covid-19 tanısı almış 48 hastayı içermektedir. Bu hastalar kurumumuza kabul edilmiş, tocilizumab ile tedavi edilmiş ve sonrasında taburcu edilmişlerdir. Bu hastaların 3. ay SARS-COV-2 spike toplam antikor seviyeleri titizlikle belirlenmiştir.
Bulgular: Çalışmanın katılımcıları, ortalama yaşları 52,5 ± 11,6 olan, yaş, cinsiyet, komorbidite ve hastanede kalış süresi ne olursa olsun 3. ayda pozitif SARS-COV-2 spike toplam antikor seviyeleri göstermiştir. Hastaların ortalama antikor seviyeleri 223,58 ± 68,36 U/mL olarak ölçülmüş, aralık 14,2 ile 250 U/mL arasında değişmiştir.
Sonuç: Bulgularımız, tüm hastaların tocilizumab tedavisi sonrası 3 ayda pozitif antikor seviyeleri sergilediklerini ortaya koymaktadır. Bu, hiperinflamasyonun Covid 19'a ikincil yönetiminde tocilizumab uygulamasının, en azından kısa vadede, antikor oluşumunu olumsuz etkilemediğini göstermektedir. Bu, gelecekteki tedavi stratejileri için önemli sonuçlar doğurabilir.

Anahtar Kelimeler: Covid 19; IL-6; Hiperinflamasyon; Tocilizumab; Antikor

Received: 27/02/2024 Accepted: 23/03/2024 Published (Online): 30/04/2024

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To cited: Karandere F, Yılmaz D, Arslan F, Şahin E, Koçoglu H, Işıksaçan N. Effect of Tocilizumab Treatment on Seroconversion in Hyperinflammation Secondary to Covid 19. Acta Med. Alanya 2024;8(1): 43-48 DOI: 10.30565/medalanya.1443962

Introduction

Severe disease due to Covid-19 can occur in healthy individuals of any age, but mostly male gender, advanced age or it is even more fatal in patients with underlying comorbidities such as cardiovascular disease (CVD), Diabetes Mellitus (DM), chronic kidney disease (CKD), Chronic Obstructive Pulmonary Disease (COPD), and cancer [1-3]. It has been observed that a hyper-inflammatory picture associated with high inflammatory markers and serum cytokine levels causes severe morbidity and mortality in a significant proportion of COVID-19 patients, with or without concomitant comorbidity [4].

Besides, it is not clear at what stage of the disease, in which patients this hyperinflammation associated with Covid-19 occurs, and when the breaking point is, it has not been revealed in the treatment algorithm yet [5]. However, cytokine inhibition and other immunomodulation treatments are applied by many centres in order to break the hyperinflammation picture [6].

While circulating IL-6 levels are extremely low in healthy individuals, a significant increase in plasma IL-6 level has been observed, especially in patients with covid-induced hyperinflammation, and it has been shown that this is strongly associated with severe disease [7-8]. In some studies, it has been observed that blocking IL-6 reduces the hyperinflammation caused by Covid-19, and Tocilizumab, an anti-IL-6 receptor antibody given for this purpose, prevents hyperinflammation in patients and positive results are obtained [9-10].

Studies hitherto for seroconversion against Covid-19 infection show that the seropositivity of antibody testing in the first week after onset of illness is unsatisfactory in many cases. However, while IgM increased at the beginning of the disease, it decreased over time, and IgG antibody reached its highest levels from the second week in many studies [11]. Xiao et al. In his study, it was shown that IgG remained positive from the 5th week, but IgM continued to decrease [12]. However, studies showing antibody response in patients using immunosuppressive agents were not observed.

Although different immunomodulators or immunosuppressive agents are used in many centres during the treatment phase of Covid-19, no study has been review in literature with the antibody responses of these patients. In our study, we detected the antibody level in the 3rd month after the disease in patients who were hospitalized in a pandemic hospital and were given 4-8mg/kg Tocilizumab at a dose of 4-8mg/kg due to hyperinflammation, and that these drugs used in patients using Tocilizumab treatment, etc. We aimed to determine whether it has an effect on antibody formation.

Material and Methods

This study is a prospective, cohort study and of 48 RT –PCR positive COVID -19 patients who were hospitalized at University of Health Science, Bakirkoy Dr. Sadi Konuk Training and Research Hospital in Istanbul, Turkey. Patients were tested for SARS –CoV–2 based on epidemiological and clinical criteria as outlined in the National Guideline for the Diagnosis and Treatment Protocol for SARS–CoV–2 Infection that was published and updated by Turkish Ministry of Health. Nasopharyngeal and oropharyngeal specimens were collected once from patients and specimens were tested for SARS–CoV–2 using real-time RT –PCR at our hospital. Informed consent was obtained from each subject prior to the study.

The Medical Research Ethics Committee of the University of Health Science, Bakirkoy Dr. Sadi Konuk Training and Research Hospital approved the study. We are committed to protecting patient privacy and complying with the Helsinki Declaration. (Ethical approval date: 02.11.2020, Approval number: 2020-22-05).

The total number of patients hospitalized in the COVID service in our hospital between October 2020 and June 2021, Tocilizumab treatment was given to 104 patients. 44 patients who bears the following exclusion criteria was excluded from work. The remaining 60 patients were called for antibody tests at the 3rd month, but 12 patients could not be contacted for various reasons. Thus, Forty-eight patients whose 3rd month antibody results were suitable for the inclusion and exclusion criteria were included into our study. Last patient was accepted in March 2021 and the study was terminated in June 2021 (See figure 1

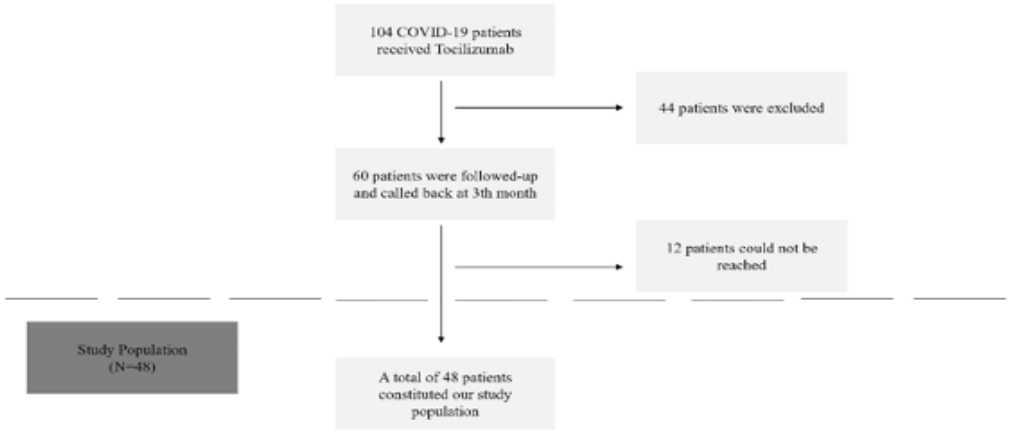

Figure 1: Flow Diagram for Study Participants From October 2020 to June 2021, 104 patients received Tocilizumab at our hospital. After excluding 44 based on specific criteria, we sought to test the remaining 60 for antibodies at 3 months. Unable to reach 12, we included 48 patients with valid antibody results in our study, which concluded in June 2021.

for study flow).

Criteria for inclusion in the study:

1- >= being over 18 years old

2- Tocilizumab treatment given during the patient's hospitalization

Exclusion criteria from the study:

1- Death status during or after treatment

2- Patients <18 years old

3- Pregnant patients

4- Refusing to participate in the study

5- The patient has no previous history of COVID

6- Receiving a different immunosuppressive treatment due to comorbidities or after discharge patients on an immunosuppressive therapy

7- Those given additional immunosuppressive therapy during COVID-19 treatment (e.g.: steroid therapy)

8- Positive real-time PCR test

9- Re-COVID-19 until the time of the 3rd month antibody test after discharge from the hospital have had an infection

10- To have had any covid 19 vaccine

A total of 48 patients constituted our study population. Demographic and clinical information was saved. The patients were invited to the hospital by phone call at the 3rd month and the antibody Blood samples were taken for levels.

Sample Collection and Testing Methods

The Elecsys Anti-SARS-CoV-2 S test is an ECLIA (electrochemiluminescence immunoassay) test used for the in vitro quantitative determination of high-affinity antibodies (including Ig G) against the SARS-CoV-2 Spike(S) protein receptor binding domain. Anti-SARS-CoV-2 measurement was performed following the manufacturer's instructions. Results are reported as numerical values in U/mL as well as non-reactive (<0.8 U/mL; negative) and reactive (≥0.8 U/mL; positive, max: 250 U/mL) results. According to the product information shared by the manufacturer, the sensitivity of the Elecsys® anti-SARS-CoV-2 test for ≥ 14 days is 100% (95% CI: 88.1% - 100%) and the overall specificity is 99.81% (95% CI). : 99, 65-99.91%).

Statistical Analysis

NCSS 2007 (Number Cruncher Statistical System, Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were used in evaluation of the study data. Frequency and percentage values of categorical variables, arithmetic mean and standard deviation values of quantitative

variables are presented.

Results

A total of 48 RT-PCR confirmed patients with COVID-19 pneumonia and who were received Tocilizumab theraphy during hospitalization period were included in the study. The mean age of the patients was 52.5 ± 11.6 years. While 87.5% (n=42) of total patients were male, 12.5% were female (n=6). Mean sPO2 at the time of admission was 91.5 ± 4.2% and mean length of hospitalisation was 25.55 ± 15.96 days (Table 1).

Table 1: Demographic characteristics of patients given tocilizumab, length of hospital stay, sPO2 at the time of admission

Gender, n (%)	
Male	42 (87.5%)
Female	6 (12.5%)
Age (years), Mean ± SD	52.5 ± 11.6
sPO2 at the time of admission (%),Mean ± SD	91.5 ± 4.2
Lenght of hospitalisation (days), Mean ± SD	25.55 ± 15.96

Of all patients, 29.2% (n=14) had hypertension; 22.9% (n=11) had diabetes mellitus; 16.7% (n=8) had COPD / Asthma; 10.4% (n=5) had CVD; 4.2% (n=2) had cancer and 10.4% (n=5) had other diseases (Table 2). Of all patients, 2.1% (n=1) had normal, 6.3% (n=3) had mild, 33.3% (n=16) had moderate, and 58.3% (n=28) had severe CT involvement at the time of admission (Table 3).

SARS-COV-2 spike total antibody levels were found to be positive at 3 months in all patients, regardless of age, gender, comorbidity and length of stay. The mean antibody levels of the patients were 223.58 ± 68.36 U/mL (min: 14.2 and max: 250 U/mL) (Table 3).

Table 2: Comorbid disease distribution of patients treated with tocilizumab

Values	Absent n (%)	Present n (%)
Hypertension	34 (70.8%)	14 (29.2%)
Diabetes Mellitus	37 (77.1%)	11 (22.9%)
Chronic obstructive pulmonary disease / Asthma	40 (83.3%)	8 (16.7%)
Cardiovascular disease	43 (89.6%)	5 (10.4%)
Cancer	46 (95.8%)	2 (4.2%)
Other diseases	43 (89.6%)	5 (10.4)

Table 3: CT involvement at the time of admission

Values	Atypical n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
CT involvement at the time of admission	1 (2.1%)	3 (6.3%)	16 (33.3%)	28 (58.3%)
3rd month SARS-COV-2 spike total antibody levels				
Patients with positive total antibody, n (%)				48 (100%)
Total antibody level (U/mL), Mean ± SD				223.58 ± 68.36

Discussion

In our study, the mean age of the patients was found to be 52.5. Of the total patients, 87.5% (n=42) were male and 12.5% were female (n=6). This situation, which was found similar to previous studies, may be associated with a higher incidence of severe Covid 19 infection in men than in women, due to reasons such as stronger immunological response in women than in men [9,13]. As in most studies, the most common comorbidity in our study was hypertension with a rate of 29.2% [14].

Many studies have shown that high levels of inflammatory markers such as crp, ldh, serum ferritin level, serum IL-6 level, etc., are associated with mortality and disease severity in Covid 19 patients [4,7]. The most striking of these inflammatory biomarkers was thought to be the rising IL-6 level [4,18].

Interleukin 6 (IL-6) produced in response to infections and tissue injuries has different biological activities. In addition to the regulation of the acute phase response, it also has the feature of inducing the differentiation of B cells into cells that secrete immunoglobulin [15-17]. For all these effects of IL-6 to occur, it must bind to the IL-6 receptor [17,18]. The detection of high serum IL-6 levels, especially in the hyperinflammation picture associated with Covid 19, drew attention to Tocilizumab, a monoclonal antibody that blocks the already existing IL-6 receptor [17]. Although its effectiveness is debated, tocilizumab has been used by many centres in the treatment of hyperinflammation associated with Covid 19, considering that it may be beneficial and life-saving in patients with COVID-19 [19-21].

In our centre, patients were managed in accordance

with the COVID 19 Guidelines determined by the Ministry of Health of the Republic of Turkey, and Tocilizumab treatment was administered to patients with hyperinflammation [22]. Understanding the duration of long-term immunological memory in Covid 19 patients after the disease is of great importance in terms of both directing vaccination studies and determining the situation of re-exposure to the disease [23]. In studies, virus-specific antibodies were detected approximately 2 weeks after the onset of COVID-19 symptoms in most patients infected with SARS-CoV-2, and although antibody levels decreased over time, it was observed that many patients remained positive in the 3rd month after infection [24, 25].

Unlike these studies, in our study, patients with hyperinflammation due to Covid 19 and who were administered Tocilizumab were selected as the patient group. SARS-COV-2 spike total antibody levels of these patients were found to be positive at 3 months, similar to other studies, regardless of age, gender, comorbidity, and length of stay. There was no negative effect of the administered dose of Tocilizumab on antibody formation, and the results were similar to those of other patients.

The development of long-term immunological memory is based on humoral and cellular immune responses. Studies have shown that vaccines administered against various viral infections in patients with diseases such as Multiple Sclerosis (MS) using immunosuppressive agents have shown that immunosuppressives reduce the humoral and cellular response [23].

In addition, in another study conducted in patients with rheumatoid arthritis, it was shown that short-term use of Tocilizumab did not reduce the humoral response of patients to Pneumococcal Polysaccharide Vaccine (PPV23) and Tetanus Toxoid Vaccine (TTV) vaccines.

In conclusion, IL-6 is an important factor in the transformation of B cells into antibody-secreting cells. Therefore, knowing the effects of IL-6 blocking on antibody formation may be important both in vaccination studies and in predicting the duration of the response to viral infections in patients using IL-6 blocking drugs for various reasons. Therefore, comprehensive multicentre studies are needed.

Conclusion

As a result of our study, we observed that antibody levels were positive in all patients at the 3rd month after Tocilizumab treatment and that Tocilizumab treatment did not have a negative effect on antibody formation, at least in the short term.

Limitations

This study has several limitations. First, we were only able to include a limited number of patients and viral load data were not available. In addition, the limited number of patients did not allow us to adjust for potential confounding factors that could influence antibody response, such as comorbidities, gender, and age. Another important limitation of our study is that it was planned to monitor antibody levels by taking blood samples from patients 3, 6, 9 and 12 months after the onset of COVID 19 symptoms. However, since the vaccination policy has changed in our country, we could only measure antibody levels in the third month after infection.

Conflict of Interest: The author reports no conflicts of interest in this work.

Funding sources: The study's research budget was funded by the Medical Specialty Training Board (TUEK).

Ethics Committee Approval: The Medical Research Ethics Committee of the Bakirkoy Dr. Sadi Konuk Training and Research Hospital approved the study, Date: 02.11.2020 and Decision No: 2020-22-05 Protocol No: 2020/407

ORCID and Author contribution: D.Y. (0000-0001-9870-5305), F.A. (0000-0001-8318-1860) and F.K. (0000-0002-7423-0170) were the primary authors who reviewed the literature and wrote the initial draft of this review manuscript. **N.I. (0000-0002-0230-6500) and H.K. (0000-0002-9208-2693)** were responsible for critical revision of the manuscript for important intellectual content. **F.K. and E.Ş. (0000-0001-6162-8983)** were responsible for analysis and interpretation data. All authors take responsibility for the accuracy and content of the manuscript.

Peer-review: Externally peer reviewed.

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