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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Secondary Infection and Co-infection in COVID-19 Patients Receiving Tocilizumab

Tocilizumab Alan COVİD-19 Hastalarında Sekonder Enfeksiyon ve Ko-enfeksiyon

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ABSTRACT *Objective:* Tocilizumab (TCZ) is a recombinant humanized anti-IL-6 receptor monoclonal antibody that is beneficial in critically ill COVID-19 patients. However, the clinical efficacy and safety of immunosuppressants (including tocilizumab, sarilumab and anakinra) in COVID-19 patients are not yet known. These treatments may predispose patients to infection. The aim of this study was to find any connection between the use of tocilizumab and increased secondary bacterial infections.

Materials and Methods: In this study, we conducted retrospective analyses of secondary bacterial infections in COVID-19 patients in the intensive care unit. This study included patients with laboratory-confirmed COVID-19 infection or clinically and radiologically confirmed COVID-19 infections who were admitted to the university hospital adult ICUs between March 2020 and January 2022. Demographic data, recent exposure and travel history, clinical symptoms or signs, laboratory findings, and comorbidities were recorded. Microbial cultures from tracheal aspirates, blood, and urine were obtained at admission and throughout the hospital stay. The patients who received tocilizumab treatment noted and analyzed for seconder infections. Blood cultures were taken at least 48 h after the first dose of tocilizumab.

Results: We found that 80 patients (%37) had positive culture samples at admission, and most of these cases were admitted to the ICU from various hospital wards. The analyzed data showed that the tocilizumab group had a higher incidence of positive culture samples (%75 vs %35, p=0,0001). The results showed that culture of tocilizumab taken patients had more incidence with metisilin resistance S. aureus, Klebsiella spp., and Acinetobacter spp. (p=0,0001). Infection and mortality rates were much higher than those in the usual care group.

Conclusion: Secondary infections and sepsis are major risk factors for mortality. The pathogens detected were drug resistant and had a lower chance of treatment. The benefit of tocilizumab treatment was lost in these patients because of secondary infections. Future studies are needed to help determine the risks of tocilizumab treatments.

Keywords: Seconder infection, COVID-19, tocilizumab

ÖZ *Amaç:* Tocilizumab (TCZ), kritik durumdaki COVID-19 hastalarında fayda sağlayan, rekombinant bir anti-IL-6 reseptörü monoklonal antikordur. Bununla birlikte, COVID-19 hastalarında immünsüpresan tedavilerin (tocilizumab, sarilumab ve anakinra dahil) klinik etkinliği ve güvenliği henüz bilinmemektedir. Bu tedaviler hastaları enfeksiyona yatkın hale getirebilir. Bu çalışmanın amacı, tosilizumab kullanımı ile artmış sekonder bakteriyel enfeksiyonlar arasında herhangi bir bağlantı bulmaktır.

Gereç ve Yöntem: Bu çalışmada yoğun bakım ünitesindeki COVID-19 hastalarında sekonder bakteriyel enfeksiyonların retrospektif analizlerini yaptık. Bu çalışmaya Mart 2020 ile Ocak 2022 tarihleri arasında üniversite hastanesinin yetişkin yoğun bakım ünitelerine kabul edilen laboratuvarca doğrulanmış COVID-19 enfeksiyonu veya klinik ve radyolojik olarak doğrulanmış COVID-19 enfeksiyonu olan hastalar dahil edilmiştir. Demografik veriler, yakın zamandaki maruziyet ve seyahat öyküsü, klinik semptomlar veya bulgular, laboratuvar bulguları ve eşlik eden hastalıklar kaydedildi. Trakeal aspiratlardan, kan ve idrardan mikrobiyal kültürler, hastaneye yatışta ve hastanede kaldıkları süre boyunca alındı. Tosilizumab tedavisi alan hastalar sekonder enfeksiyonları not etmiş ve analiz etmişlerdir. Kan kültürleri ilk tosilizumab dozundan en az 48 saat sonra alınmıştır.

Bulgular: 80 hastada (%37) başvuru sırasında kültür örneğinin pozitif olduğunu ve bu olguların çoğunun çeşitli hastane servislerinden yoğun bakıma kabul edildiğini saptadık. Analiz edilen veriler,

tosilizumab grubunun pozitif kültür örnekleri insidansının daha yüksek olduğunu gösterdi (%75'e karşı %35, p=0,0001). Sonuçlar, tosilizumab kültürü alan hastalarda Metisilin direnci insidansının daha yüksek olduğunu göstermiştir. S. Aureus, Klebsiella spp. ve Acinetobacter spp. (p=0,0001). Enfeksiyon oranı ve ölüm oranı normal bakım grubundan çok daha yüksekti.

Sonuç: Sekonder enfeksiyonlar ve sepsis mortalite için önemli bir risktir. Tespit edilen patojenler ilaca dirençliydi ve tedavi şansı daha düşüktü. Bu hastalarda sekonder enfeksiyonlar nedeniyle tocilizumab tedavisinin yararı kaybolmuştur. Tosilizumab tedavilerinin risklerini belirlemeye yardımcı olmak için gelecekteki çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Sekonder enfeksiyon, COVID-19, tocilizumab

Introduction

Most of the COVID- 19 patients are asymptomatic or have symptoms that don't need hospitalization. However, there are patients who develop a respiratory failure requiring oxygen support and hospital care. Many of them need intensive care unit (ICU) admission and ventilator support (1). In these patients, COVID has a progressive clinical characteristic. The disease usually begins as an upper respiratory tract infection. Following days, patients have rapid deterioration and increased oxygen support. This results acute respiratory distress syndrome (ARDS), multi-organ failure and death (2).

The pathogenesis of COVID- 19 is thought a dysregulated inflammatory response causing clinical manifestations in patients (3). This systemic response includes massive releasing of cytokines such as interleukin (IL)-1, IL-6 (4). This process causes alveolar damage and microvascular thrombosis (5). Treatment of COVID-19 focuses on stopping hyperinflamation response using corticosteroids and immune suppressive agents.

Tocilizumab (TCZ) is a recombinant humanized anti-IL-6 receptor monoclonal antibody that inhibits the binding of IL-6 to both membrane and soluble IL-6 receptors, blocking IL-6 signaling and reducing inflammation. The drug is used in rheumatoid arthritis, juvenile inflammatory arthritis and refractory giant cell arteritis (6). Tocilizumab is also approved for systemic inflammatory response caused by the massive release of proinflammatory cytokines (7,8). TCZ was tested in many COVID-19 cases due to these characteristics and shown that many laboratory parameters improved such as C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin and Total leukocyte Count (TLC). TCZ usage in severe COVID-19 patients causes less complications, decreased duration of hospitalization, decreased needs for ICU admission (9).

Secondary infections are common in viral respiratory diseases. There are studies that shows secondary bacterial infection (SBI) is seen %5-15 of patients with COVID-19. According to reports, 50% of COVID-19 deaths had history of SBIs. SBIs have a higher risk of mortality (10). Using immune suppressive treatment makes patients proned to SBI. In most cases, benefit of avoiding pulmonary fibrosis due to COVID infection more beneficial then avoiding SBI.

In this study, we conducted a retrospective analysis of SBIs in COVID-19 patients at intensive care unit. The aim of this study is to find any connection between usage of tocilizumab and increased SBI in these patients. This connection may lead better clinical follow-up and making health providers aware of SBI risk.

Materials and Methods

The permission for this retrospective study had taken from Ethics Committee of our institute.

This study included patients with laboratory-confirmed COVID-19 infection or clinical and radiological confirmed COVID-19 infection who were admitted to the university hospital adult ICUs between March 2020 and January 2022. The diagnosis of COVID-19 was determined by a positive result on a reverse-transcriptase–polymerase-chain reaction (RT-PCR) assay or antibody Rapid Test of a specimen collected on a nasopharyngeal swab or endotracheal aspirate. Patient's data was obtained from electronic data stored in software in the hospital computers.

Data Collection

Demographic data, the recent exposure and travel history, clinical symptoms or signs, laboratory findings and comorbidities were recorded. Acute Physiology and Chronic

Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were calculated and recorded. Invasive mechanical ventilation parameters were also recorded. Radiologic assessments included chest radiography or computed tomography (CT), was performed

at admission and as needed. Arterial partial pressure of oxygen (PaO2), PaO2/FiO2 ratio and acute respiratory distress syndrome (ARDS) were documented.

Sepsis and septic shock were defined and managed according to established guidelines [11] and the Turkey

Ministry of Health recommendations for treatment of COVID-19 patients [10].

Microbial cultures from tracheal aspirates, blood and urine were taken at admission and throughout the hospital stay. The patients evaluated with infection diseases departments and rheumatology departments for tocilizumab treatment. The patients who took tocilizumab treatment had noted and analyzed for seconder infections. The blood cultures had taken at least 48 hours after first dose of tocilizumab. The patients discharge status (dead, alive), and length of stay in the ICU were also recorded.

Statistical Analysis

All statistical analyses were performed using SPSS 25.0 (IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.)). Continuous variables were defined by the mean ± standard deviation and categorical variables were defined by number and percent. Difference between categorical variables were analyzed with Chi Square analysis. Statistical significance was determined as p<0,05.

Results

Two hundred and sixteen patients admitted to ICU with laboratory confirmed COVID-19 infection between March 2020 and January 2022.

%66.7 of the patients were male. Mean age was 65.93 ± 14.45 years. %49.1 of the patients admitted to ICU from emergency service and the others were from COVID-19 wards and other wards. One or more comorbidities was found in 192 patients. 24 patients had no comorbidity. 338 comorbidities had detected in these patients. Hypertension was the most common comorbidity in these patients (%44,4). Diabetes mellitus (%38) and oncological diseases (%17,6) followed hypertension (Table-1). The infection parameters at admission are shown at Table 1.

Sixty patients were intubated at beginning of admission (%27,7). Forty patients were intubated in course of admission. One hundred and sixteen patients were followed with HFNO and non-invasive mechanic ventilation (%53,7). HFNO and NIMV administered alternately. Sixteen patient who received tocilizumab were intubated which only one of them survived and discharged.

At the admission, empiric antibiotics were started by Infection Diseases Department according to laboratory and clinical findings. 33 patients didn't receive any empiric treatment. Tigecycline, piperacillin-tazobactam and ceftriaxone were the most chosen options in treatment. The microbial samples of patients had taken at admission. 80 patients had positive culture. %94 of these cultures were blood samples. Most common pathogens were coagulase negative staphylococcus, methicillin resistant staphylococcus aureus and enterococcus spp. After positive culture samples, empiric treatment had changed according to antimicrobial resistance testing in 28 patients (%13). The microbiological findings and treatments at admission is shown at Table 2.

Patients with macrophage activation syndrome who have no or little response to glucocorticoids had treated with tocilizumab (humanized monoclonal antibody against the interleukin-6 receptor). The dosage used for tocilizumab is 8 mg/kg (patients ≥30 kg) or 12 mg/kg (patients <30 kg) as a single dose (maximum: 800 mg/dose). Tocilizumab treatment was decided with the cooperation of Infection Diseases Department and Rheumatology Department. 24 of 216 patients has taken tocilizumab treatment with approvement of Turkish Health Ministry.

18 of 24 patients who taken tocilizumab treatment, had worsened clinical conditions and increased level of infection markers. Culture samples were taken. Methicillin resistance S. Aureus (n=11) Klebsiella spp. (n=6) and Acinetobacter spp. (n=6) were most common in these patients.

Table 1. Demographics and clinical characteristics of the patients

Age (mean ± SD)	65.93±14.45
Sex (M/F)	144 (66.7%) /72 (33.3%)
SOFA score (mean ± SD)	2.6±1.32
Admission service (Emergency/other wards)	106 (49.1%) /110 (50.9%)
Length of ICU stay (day) (mean ± SD)	11.17±9.77
Exitus	94 (43.5%)
Comorbidities	
Hypertension	96 (44.4%)
Diabetes mellitus	82 (38%)
Oncological diseases	38 (17.6%)
Cardiac failure	20 (9.3%)
Coronary artery disease	19 (8.8%)
Hematological disease	13 (6%)
Laboratory findings at admission	
Procalcitonin (mean ± SD)	2.9±10.51
C-reactive protein (mean ± SD)	123.83±86
Ferritin (mean ± SD)	1023.33±1335.09
SD: Standard deviation	

Almost all of the patients needed to repeat cultures due to clinical and laboratory worsening. 57 of patients who didn't receive anti-cytokine treatment had positive result in their cultures. The pathogens were Methicillin resistance S. Aureus (n=28) Klebsiella spp. (n=10) and Acinetobacter spp. (n=10), Enterococcus spp. (n=8), Pseudomonas spp. (n=6), Candida spp. (n=3).

The difference of clinical and microbiological characteristics is shown at Table 3. The results have compared between patients who received tocilizumab and who didn't. There was no statistical difference in cultures at admission. There was an increased positive rating in cultures that were utilized after clinical worsening (p= 0,0001). The results showed that culture of tocilizumab taken patients had more incidence with Methicillin resistance S. Aureus, Klebsiella spp. and Acinetobacter spp. (p=0,0001). Death was more common in tocilizumab group. There was no difference in admission service.

Table 2. Microbiological findings at admission and antimicrobial treatment characteristics	
Positive culture samples (poz/neg) (total n=216)	80 (37%)/136 (63%)
Pathogens at culture positive patients	
Coagulase negative *Staphylococcus*	35 (43.8%)
Methicillin resistant *Staphylococcus aureus*	33 (41.3%)
Enterococcus spp.	7 (8.8%)
Klebsiella spp.	3 (3.8%)
Corynebacterium spp.	3 (3.8%)
Candida spp.	2 (2.5%)
Acinetobacter spp.	1 (1.3%)
Pseudomonas spp.	1 (1.3%)
Other pathogens	5 (6.3%)
Positive sample location	
Blood	78 (97.5%)
Tracheal aspiration	4 (5%)
Urine	1 (1.3%)
Empiric treatment at admission	
Tigecycline	66 (12%)
Piperacillin-tazobactam	50 (9.1%)
Ceftriaxone	42 (7.6%)
Meropenem	17 (3.1%)
Teicoplanin	14 (2.5%)
No antibiotics	33 (6%)

Discussion

After COVID-10 outbreak, many immunocompromised patients were admitted to ICUs. There has been an increased need of ICUs. Many of these patients had secondary bacterial infections and ICU specialists fought with sepsis and co-infection beside COVID-19. There are many studies, reviews and case report about secondary infections in COVID. The mechanism of increased secondary bacterial infection thought to be the failure of the adaptive immune reaction toward viral infection against bacterial infection (13).

In one study, researchers utilized the data of 1495 cases and %6.8 of these cases had secondary bloodstream infections. The pathogens in these cases were mostly gram-negative bacteria such as Acinetobacter Baumanii (%35.8) and Klebsiella Pneumonia (%30.8) (10). In a study, hang et al. analyzed 148,221 patients with SARSCoV-2 pneumonia were admitted to Zhongnan Hospital, Wuhan, China. 25.8% (57/221) patients had co-infections, 29.8% (17/57) of these cases were co-infected with bacteria (14).

In our study, secondary infection rate was higher like these studies. 80 patients (%37) had positive culture sample at admission and most of these cases was admitted to ICU from various hospital wards. The reason for high rate of positive cultures at admission is thought to be long duration of hospital admission. Most patients had come to ICU after being in infection wards for days. Most of the positive cultures had the pathogens such as coagulase negative staphylococcus, methicillin resistant staphylococcus aureus and enterococcus spp. Most of our patients had worsened clinically (fever, decreased consciousness) and had cultures repeated. 75 of these patients (%35) had secondary bacterial infection with positive cultures. These results are consistent with other studies.

There are limited studies about secondary infections in patients who take anti-cytokine, anti-inflammatory treatment. It is known that these treatments cause predisposition with secondary infections. Tocilizumab is most used immunomodulatory treatment in our ICU. These patients evaluated about infections, immunosuppressive conditions, tuberculosis, HIV. After this evaluation, tocilizumab admitted.

The analyzed data showed that tocilizumab group has a higher incidence of positive culture samples (%75 vs %35, p=0,0001). Methicillin resistance S. Aureus, Klebsiella spp. and Acinetobacter spp. had increased incidence in tocilizumab group's cultures against usual care group's

Table 3. Comparison of clinical and microbiological characteristics				
		Tocilizumab group	Non-tocilizumab group	p-value
Admission service	Emergency	12 (%50)	94 (%48.96)	0.923
	Wards	12 (%50)	98 (%51.04)	
Outcome	Discharge	9 (%37.5)	113 (%58.85)	0.047*
	Death	15 (%62.5)	79 (%41.15)	
Cultures	Negative	6 (%25)	153 (%79.69)	0.0001*
	Positive	18 (%75)	39 (%20.31)	
Coagulase negative *Staphylococcus*	Negative	209 (%96.76)	187 (%97.4)	0,176
	Positive	7 (%3.24)	5 (%2.6)	
Methicillin resistance *S. aureus*	Negative	13 (%54.17)	175 (%91.15)	0.0001*
	Positive	11 (%45.83)	17 (%8.85)	
Corynebacterium	Negative	22 (%91.67)	187 (%97.4)	0,176
	Positive	2 (%8.33)	5 (%2.6)	
***Klebsiella* spp.**	Negative	18 (%75)	188 (%97.92)	0.0001*
	Positive	6 (%25)	4 (%2.08)	
***Acinetobacter* spp.**	Negative	18 (%75)	188 (%97.92)	0.0001*
	Positive	6 (25%)	4 (2.08%)	
***Enterococcus* spp.**	Negative	20 (83.33%)	188 (97.92%)	0.006*
	Positive	4 (16.67%)	4 (2.08%)	
***Pseudomonas* spp.**	Negative	22 (91.67%)	188 (97.92%)	0.135
	Positive	2 (8.33%)	4 (2.08%)	
***Candida* spp.**	Negative	23 (95.83%)	190 (98.96%)	0.299
	Positive	1 (4.17%)	2 (1.04%)	
*p<0.05 statistically significant; chi-square test				

(respectively, %45- %8, %25-%2 and %24-%2; p=0,0001 for each).

Giacobbe et all., studied secondary bloodstream infections among critically ill patients with COVID-19. They found the cumulative risk of BSI was 25% after 15 days and 50% after 30 days of ICU stay. The study also showed that Tocilizumab was associated with an increased risk of secondary infection (p=0.003) (15). Our data is consistent with these ratios.

RECOVERY study showed that the patients receiving tocilizumab has higher chance for discharge at 28 day of admission and lower rates for mortality and mechanic ventilation needs. RECOVERY study didn't analyze infection situation in patients (6).

In one study, receiving tocilizumab was associated with a higher risk of secondary bacterial (48.1 vs. 28.1%; p = 0.029 infections and higher mortality (35.2 vs. 19.3%; p = 0.020) (16). Our mortality rate is higher in tocilizumab group consistent with higher positive culture rates (%62 vs %41, p=0,004). Our results are similar with this study.

In our study, infection rate and mortality rate were much higher than usual care group. Secondary infections and sepsis are a major risk for mortality. The pathogens detected were drug-resistance and had a lower chance of treatment. The benefit of tocilizumab treatment lost in these patients because of secondary infections.

Another reason for higher mortality is thought to need of mechanic ventilation. Our data showed that %66 of the patients who received tocilizumab were intubated. Only one of them survived and discharged while other patients were lost. Mechanic ventilation is a major risk for both infection and mortality. This is also a controversial point. Tocilizumab prones to infection but tocilizumab is given to patients who are in severe condition like need of mechanic ventilation. Further studies are needed in more specific groups on this subject.

In an ongoing study, the mortality rate in tocilizumab-treated patients was 24.1%. There was an association between mortality and seniority, the need for mechanic support, the presence of critical COVID-19 and severe lung parenchymal disease. The same study found that invasive MV support, immunosuppression and extended lung injury may increase the risk for secondary bacterial infections (17).

This study has several limitations: small sample size, retrospective nature (selection and information biases) and single-center nature (contamination and flora of the same ICU).

Conclusion

The incidence rate of secondary bacterial infection is higher in critically ill patients in COVID-19. Tocilizumab is a promising treatment for COVID patients who has overactive immune system due to cytokines. In response to this, tocilizumab can create predisposition to infection which causes sepsis and mortality. These risks cast a suspicion of benefit in tocilizumab treatment. These findings should be confirmed with a larger randomized clinical trial with longer follow-up. Future studies are needed to help determine about risks of tocilizumab treatments.

Ethics

Ethics Committee Approval: The permission for this retrospective study had taken from Non-invasive Research Ethics Committee of Pamukkale University.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ç.E., H.S., Design: Ç.E., H.S., Data Collection and Process: Ç.E., M.K., B.Ş., Analysis or Interpretation: Ç.E., M.K., H.S., Literature Search: Ç.E., M.K., Writing: Ç.E.

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