Success of the Cytokine Absorption Therapies in COVID-19 Patients Diagnosed with Cytokine Release Syndrome

Huseyin Ozkarakas[1], Murat Arslan[1], Mehmet Ugur Bilgin[1], Alpay Ari[2], Nuri Arda Ertem[1] and Zeki Tuncel Tekgul[1]

[1]*Department of Anesthesiology and Reanimation, Intensive Care Unit, University of Health Sciences, Izmir Bozyaka Training and Research Hospital, Izmir, Turkey*

[2]*Department of Infectious Diseases, University of Health Sciences, Izmir Bozyaka Training and Research Hospital, Izmir, Turkey*

ABSTRACT

Objective: To compare the effects of cytokine absorption therapy with a resin-based cytokine absorption cartridge to tocilizumab treatment in critically ill COVID-19 patients diagnosed with cytokine release syndrome (CRS).

Study Design: A descriptive study.

Place and Duration of Study: University of Health Sciences, Izmir Bozyaka Training and Research Hospital, Izmir, Turkey from April 2020 to April 2021.

Methodology: Twenty-four intensive care unit (ICU) patients were included in the study. Inclusion criteria were diagnosis of severe COVID-19, diagnosis of CRS and age of older than 18 years. Exclusion criteria were pregnancy, malignancy, prior COVID-19 vaccination, procalcitonin levels higher than 2 ng/ml and life-threatening comorbidities before ICU admission. Twelve patients received tocilizumab and the other 12 patients received cytokine absorption therapy. The groups were compared for clinical outcomes and inflammatory markers (CRP, fibrinogen, ferritin, D-dimer).

Results: Inflammatory markers showed smilar changes with both treatments, mostly toward improvement, on the same post-treatment days. The mortality rate was 58% (seven patients) in the cytokine absorption group and 50% (six patients) in the tocilizumab group (p = 0.682).

Conclusion: It was found that the cytokine absorption therapy reduces inflammatory mediators in intubated and critically ill Covid-19 patients similar to tocilizumab treatment, and both treatments have comparable clinical outcomes.

Key Words: *SARS-CoV-2, Cytokine release syndrome, Chemokines, Absorption, Tocilizumab*.

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INTRODUCTION

Despite all efforts, effective treatment for coronavirus disease 2019 (COVID-19) is yet to exist. Treatment today includes symptomatic and supportive therapies or experimental medicines. Although most patients experience flu-like symptoms such as fever, cough, shortness of breath, and myalgia, some of them suffer acute respiratory distress syndrome (ARDS) or even multiple organ dysfunction syndrome (MODS), which populously lead to death. MODS in severe patients is usually preceded by the cytokine release syndrome (CRS) that commonly presents with a rise in pro-inflammatory cytokines and inflammatory markers (especially interleukin-6/IL-6).[1-4] Timely treatment of the CRS may decrease MODS and mortality.

Correspondence to: Dr. Huseyin Ozkarakas, Department of Anesthesiology and Reanimation, Intensive Care Unit, University of Health Sciences, Izmir Bozyaka Training and Research Hospital, Izmir, Turkey
E-mail: h.ozkarakas@hotmail.com

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Laboratory results usually show elevated CRP, ferritin, procalcitonin, and D-dimer, particularly with a rise in IL-6 levels.[5] CRS treatments either aim to reduce the effects of cytokines or remove the excessive cytokines from the circulation. Medicine such as colchicine, corticosteroids, Il-1 or Il-6 receptor inhibitors, and Janus Kinase (JAK) enzyme inhibitors reduce the effects of cytokines.[6] Extracorporeal blood purification (EBP) procedures help with the removal of the excessive inflammatory cytokines.[7,8]

In this study, the aim was to compare tocilizumab treatment to cytokine absorption in reducing the inflammatory mediators in COVID-19 patients diagnosed with CRS.

METHODOLOGY

Intensive care unit (ICU) patients, who were diagnosed with COVID-19 and CRS, and treated with either tocilizumab or extracorporeal blood purification (EBP). COVID-19 diagnoses were based on a real-time polymerase chain reaction (real-time PCR); and CRS diagnoses were made according to HLH 2009 criteria.[9] Inclusion criteria were severe COVID-19, CRS diagnosis, and age of older than 18 years. Exclusion criteria were

pregnancy, malignancy, prior COVID-19 vaccination, procalcitonin levels higher than 2ng/ml and life-threatening comorbidities before ICU admission.

The study was conducted at the University of Health Sciences Izmir Bozyaka Training and Research Hospital and case search was limited to one year, from April 2020 to April 2021. Patient files and the hospital's data management system were used to gather data; and approval of the local Ethics Committee was received with the number 2021/103 dated 23rd June 2021.

Tocilizumab patients received the treatment twice, at 12 hours interval, 8 mg/Kg as intravenous infusion. Cytokine absorption therapy was applied with HA330-II - disposable hemoperfusion cartridge (HA330 resin, styrene-divinylbenzenecopolymers, once a day for two hours, during three days. Blood flow was set to 100-250 ml/min. Both the treatments were initiated immediately after when CRS diagnosis was made.

The selection of the treatment for those patients was based on the availability of the tocilizumab/anakinra. The hospital pharmacist was inquired about drug availability after CRS diagnosis; and if neither of the agents would be accessible for the following 24 hours, the cytokine absorption method was executed.

Other treatments for COVID-19 patients included oral antiviral drugs (favipiravir), low molecular weight heparin, and 40 mg per day intravenous methylprednisolone. Routine antibiotic therapy was not part of this study protocol.

All of the 12 patients in the cytokine absorption group were included in the study. To achieve evenly-matched groups, tocilizumab patients were sorted by the date of admission to the ICU; and the first of each five patients were included in the study (1st, 6th, 11th, and so). Therefore, two groups were formed with 12 patients in each group. Age and gender data, comorbidities, APACHE-II scores, length of stay in ICU (LoS), length of mechanical ventilation (LoMV) and mortality data were collected. CRP, D-dimer, ferritin, and fibrinogen values were compared for each day after the treatment to the value before the treatment, per this equation: (Before treatment value)-(value on that particular day) / (before treatment value). Increase or decrease in the values in each day were given as percentages and statistically analysed between two groups. Patients were grouped according to their admittance APACHE-II scores (0-10 / 11-20 / 21-30 / 31 or more) to check the groups against the disparity. SPSS (Statistical Package for Social Sciences) version 21, (IBM) was used for statistical analysis. The compliance of the data to normal distribution was determined by the Shapiro-Wilk test. Normally distributed quantitative data were given as mean and standard deviation. Non-normally distributed data were given as median and interquartile range. Categorical data were given as number and/or percentage. Differences of mean or median values were calculated using the Student's t-test (for normally distributed data) or Mann-Whitney U-test (for non-normally distributed data). Categorical data were evaluated using the Chi-Square test. The significance level was taken as $p < 0.05$.

Table I: Patients' characteristics.

	Cytokine Absorption Group (n = 12)	Tocilizumab Group (n =12)	p-value
Age[a, g]	52.08 ± 14.74	54.17 ± 14.39	0.729
Gender[b, e]			
Male	7 (58.3%)	8 (66.7%)	0.673
Female	5 (41.7%)	4 (33.3%)	
Comorbidities[b, e]			
Diabetes Mellitus	5 (41.7%)	5 (41.7%)	
Hypertension	4 (33.3%)	5 (41.7%)	0.931
Renal Injury	1 (8.3%)	1 (8.3%)	
Haematological Disorders	2 (16.7%)	1 (8.3%)	
APACHE - II Scores[b, e]			
0-10	-	-	
11-20	2(16.7%)	4 (33.3%)	0.607
21-30	3(25%)	3 (25%)	
>31	7(58.3%)	5 (41.7%)	
Urea[d, f](mg/dl)	46 [109]	45 [121]	0.642
Creatinine[d, f](mg/dl)	1.12 [1.41]	1.12 [3.75]	1.00
Procalcitonin[d, f](ng/ml)	0.36 [0.82]	0.24 [0.78]	0.813
AST[d, f](U/L)	49.50 [91.25]	49.50 [120]	0.749
ALT[d, f](U/L)	49.00 [67.00]	65.00 [75.50]	0.908
Length of Mechanical Ventilation[d, f]	9.5 [19]	12 [12]	0.352
Length of Stay in ICU[d, f]	12.5 [36]	16 [8]	0.794
Mortality[b, e]	7 (58%)	6 (50%)	0.682

[a] Mean ± standard deviation, [b] number and %, [d] median [interquartile range], [e] chi square test, [f] Mann-Whitney U test, [g] Student's t-test, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase.

RESULTS

Mean age was 52.08 ± 14.74 years in the cytokine absorption group and 54.17 ± 14.39 years in the tocilizumab group (p = 0.729). Gender distribution, comorbidities and laboratory values were presented in Table I.

The groups were compared for APACHE-II scores, length of stay in ICU, and length of mechanical ventilation, which were found to be similar in the analyses (Table I).

Change of the inflammatory markers (CRP, fibrinogen, ferritin, D-dimer) were given in Table II. Both treatment methods caused statistically similar changes, mostly toward improvement, on the same days.

The mortality rate was 58% (seven patients) in the cytokine absorption group and 50% (six patients) in the tocilizumab group (Table I).

DISCUSSION

The treatment for the COVİD-19 patients mainly consists of supportive therapies. For example, COVİD-19 patients diagnosed with ARDS receive protective lung ventilation, optimal positive end-expiratory pressure (PEEP) titration, and prone positioning. As mentioned before, CRS is a preceding syndrome for MODS; and IL-6 plays a key role in its pathophysiology, along with other proinflammatory mediators.[8,10]

Tocilizumab reduces the levels of proinflammatory cytokines and severeness of CRS symptoms. A study with 21 patients reported a swift drop in symptoms like fever and no serious adverse effects.[11] Similarly, these results showed no adverse effects with tocilizumab, and the seconder pulmonary infection rate was comparable to the cytokine absorption group.

Table II: Post-treatment values.

	Cytokine Absorption Group (n = 12)		**Tocilizumab Group (n =12)**		**p-value[a]**
C-Reactive Protein (mg/Lt)	*Value*	*Change[b]*	*Value*	*Change[b]*	
Pre-Treatment	233 [109.3]	-	307 [164.3]	-	-
Post-Treatment Day 1	201 [105]	0.025 [0.44]	280 [228.5]	0.315 ± 0.34[c]	0.104
Post-Treatment Day 2	160 [116]	0.36[0.36]	190.5 [89.3]	0.515 ± 0.25[c]	0.353
Post-Treatment Day 3	110 [32]	0.55 [0.44]	104 [47]	0.59 [0.34]	0.908
Fibrinogen (mg/dl)					
Pre-Treatment	452 [319]	-	598 [390.5]	-	-
Post-Treatment Day 1	379.5 [198.3]	0.23 [0.18]	379.5 [335.3]	0.02 [0.31]	0.041
Post-Treatment Day 2	346 [55]	0.30 [0.27]	339 [141.8]	0.14 [0.95]	0.055
Post-Treatment Day 3	320 [85.5]	0.43 [0.29]	308 [120]	0.26 [0.74]	0.116
Ferritin (µg/L)					
Pre-Treatment	1500 [0]	-	1500 [604]	-	-
Post-Treatment Day 1	1480 [82]	0.0 [0.16]	1328 [553]	0.01 [0.05]	0.174
Post-Treatment Day 2	1220 [374.5]	0.19 [0.30]	991 [542]	0.19 [0.30]	0.726
Post-Treatment Day 3	948 [495.8]	0.37 [0.34]	618 [581.3]	0.37 [0.38]	0.771
D-Dimer (ng/mg)					
Pre-Treatment	2823.5 [3729.5]	-	3103.5 [5398.5]	-	-
Post-Treatment Day 1	2956 [1472.5]	-1.34 [4.63]	2923 [5233.3]	0.11 [4.52]	0.450
Post-Treatment Day 2	2089 [1048]	-0.32 [3.58]	2557.5 [2418.8]	0.35 [4.21]	0.416
Post-Treatment Day 3	1991 [1396]	0.15 [3.07]	2196 [1876.8]	0.45 [3.12]	0.384

**All variables are expressed as median [interquartile range] if not stated otherwise. [c] Mean ± standard deviation, [a]p value were obtained by comparing the changes on that particular day. [b]Equation of Change: (Pre-treatment value-value on that particular day) / Pre-treatment value. **Mann-Whitney U-test was used for the statistical analysis of equation of change.*

CRS in COVID-19 patients is the result of excessive production of proinflammatory cytokines, IL-6 in particular.[12-14] This led to presumption that tocilizumab might do a better job in preventing CRS. As for the cytokine absorption methods, removing all cytokines from the circulation, as in non-selective adsorption cartridges, raise questions of its advantages against its disadvantages.[7]

Studies reporting the effectiveness of tocilizumab in COVID-19 patients with CRS coexist with studies claiming that it has no benefit compared to placebo in mortality, rate of admittance to ICU, and mechanical ventilation need.[15] This study also marked no statistical difference in mortality, length of mechanical ventilation, and length of ICU stay between the tocilizumab and the cytokine absorption groups. However, there is no data regarding the effectiveness of either method in these parameters since the study lacks a placebo group.

A study by Asgharpour *et al*., states that the cytokine absorption method reduces IL-6 levels but this is statistically not different between mortal and non-mortal patients.[7] The study centre is not equipped to measure levels of IL-6 or any cytokines; but measurement of inflammatory markers such as CRP, D-dimer, ferritin, and fibrinogen is routinely achievable. Comparing these measurements, no statistical difference was detected in these markers between the two groups.

The most frequent comorbidities of COVID-19 patients in the ICU were hypertension, chronic kidney failure, chronic obstructive pulmonary disease (COPD), cardiovascular diseases, and diabetes mellitus (DM). An earlier report stated that 20-40 % of COVID-19 patients in the ICU developed kidney damage during their course.[16] Some of the extracorporeal blood purification methods have the ability to combine cytokine absorption with hemodiafiltration and some of the cytokine absorption cartridges can be used simultaneously in a hemodialysis machine. This is potentially valuable in COVID-19 patients, who need renal replacement therapy. Extracorporeal membrane oxygenation (ECMO) is another option for combination therapy and it could be effective in selected patients. The flexibility of application and the ability to treat multiple conditions at a time might be a major advantage of extracorporeal blood purification therapies. However, due to the small sample group, this study is unable to distinguish any real advantages of EBP over tocilizumab treatment.

Large number, randomised and controlled studies are needed to fully evaluate the effectiveness of cytokine absorption methods. However, the authors believe that these methods must be considered in case of cytokine release syndrome if the tocilizumab is inaccessible or the patient needs another extracorporeal treatment method.

CONCLUSION

It was found that cytokine absorption with HA330-II cartridge reduces inflammatory mediators in intubated and critically ill COVID-19 patients similar to tocilizumab treatment.

ETHICAL APPROVAL:

Approval of the local Ethics Committee was received with No. 2021/103 dated 23rd June 2021.

PATIENTS' CONSENT:

This study was designed retrospectively. The information

required for the study was obtained from the data processing unit of the hospital. Therefore, patients' consent was not obtained.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
HO: Analysis, design of the work, writing the manuscript.
MA: Analysis, critical revision.
MUB: Design of the work, interpretation of data for the work, translation.
AA: Drafting the work or revision.
NAE: Interpretation of data for the work.
ZTT: Analysis, final approval of the version to be published.

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