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RESEARCH ARTICLE

EFFECTS OF TOCILIZUMAB AND SYSTEMIC CORTICOSTEROIDS IN PATIENTS WITH CARDIOVASCULAR DISEASE ON CLINICAL OUTCOMES IN COVID-19

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Abstract

Background: COVID-19 is a respiratory disease caused by a novel coronavirus, with a high mortality, especially in patients with underlying diseases. Patients with COVID-19 pneumonia may express an immune response such as cytokine storm or macrophage activation syndrome, which can lead to organ failure and death.Some studies suggest that corticosteroid and tocilizumab can improve the respiratory status and clinical outcome of patients with COVID-19 pneumonia.
Aim: The aim of the study was to determine the potential effect of the use of tocilizumab and corticosteroids in patients with concomitant cardiovascular diseases on the clinical course and outcome during COVID-19 infection.
Methods: We performed an observational retrospective study of adult patients admitted to "Travnik" and "Jajce" Hospital, Bosnia and Herzegovina, between 01.03.2020 and 01.12.2022 with confirmed COVID-19 and underlying cardiovascular disease (CVD).
Results: The majority of patients (110 or 60.4%) had previously reported cardiomyopathy, and other cardiovascular disease included earlier myocardial infarction, stroke, cardiac arrhythmias, cardiac surgery, compensated cardial disease, and acute myocardial infarction. Total of 159 (87.4%) patients received corticosteroids during treatment. Tocilizumab has been used in 16 patients; nine survived and seven died.
Conclusion: Even some studies proved that it might improve clinical presentation and prevent lethal outcomes; in our study there were no significant results to confirm this thesis.
Keywords: COVID-19, corticosteroids, respiratory disease, tocilizumab.

INTRODUCTION

COVID-19 is a respiratory disease caused by a novel coronavirus, with high mortality, especially in patients with underlying diseas[1]. Most people with COVID-19 will have a mild form of disease, but older patients, males and those with comorbidity have a higher risk for an unfavourable outcome[2]. Patients with COVID-19 pneumonia can express immune response such as cytokine storm or macrophage activation syndrome, which can lead to organ failure and death[3]. Previous studies reported a strong association between underlying cardiovascular diseases and bad prognosis for COVID-19 patients[4]. Tocilizumab is a monoclonal antibody against interleukin-6, and it is used for the therapy of some inflammatory disease[5]. Some studies suggest that Tocilizumab can improve the respiratory status and clinical outcome of patients with COVID-19 pneumonia[6]. Corticosteroids are widely in use for the treatment of COVID-19 patients; even their role in the therapy is still controversial. In some studies there was no significant decrease in mortality after use of high dose of dexamethasone[7].

The aim of the present study was to determine the potential impact of tocilizumab and corticosteroid use in patients with concomitant cardiovascular disease on the clinical course and outcome during COVID-19 infection.

SUBJECTS AND METHODS

We conducted an observational retrospective study of patients admitted to "Travnik" and "Jajce" Hospital, Bosnia and Herzegovina, between 1 March 2020 to 1 December 2920. Inclusion criteria were PCR confirmed diagnosis of COVID-19, age of patients 18

years and above, medical record of previously diagnosed of underlying cardiovascular disease (CVD). Data necessary for the study were retrieved from the patient's history: age, sex, duration of symptoms before hospitalisation, need for oxygen support with facial mask, corticosteroids and tocilizumab use, developed complication, requirement for invasive ventilation, and the outcome of disease. Among 355 hospitalised patients, 182 of them had one or more CVD. We collected clinical and demographic data including cardiovascular comorbidities, use of tocilizumab and systemic corticosteroids, complications, and outcomes of the disease. The statistical analysis of data was done by SPSS version 24 statistical program and Microsoft Excel version 11. Level of $p<0.05$ considered as statistically significant. After statistical analysis, results were presented by tables and graphicons. The research was approved by the Ethics Committee of the both medical centres.

RESULTS

Among 355 analysed histories of admitted patients with COVID 19, 182 met inclusion criteria. Infection with SARS-COV-2 virus was confirmed with PCR analysis. All patients had COVID-19 pneumonia, verified by chest X-ray of CT scan. There were 113 (62%) male and 69 (39%) female patients (Figure 1).

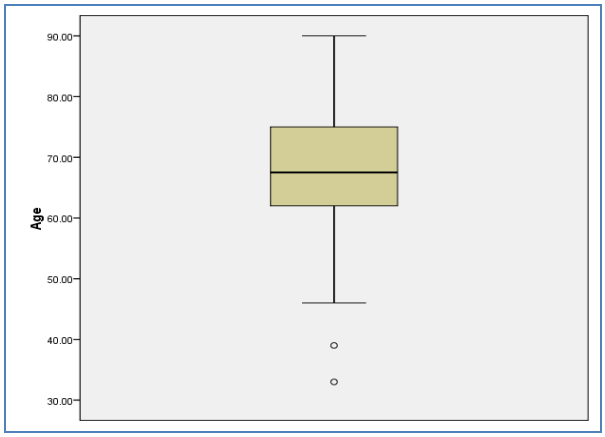

Figure 1: **Age of the patients.**

The median age of the patients was 67.5, ranged 33 – 90 years. Median prehospital time was 7 days, in the range of 3-14 days. The majority of patients (110 or 60.4%) had a previously registered cardiomyopathy, and other CVD included earlier myocardial infarction, stroke, arrhythmias, cardiac surgery, compensated cardial disease, and acute myocardial infarct.

Values of CRP range from 3 mg/dl to 403 g/dl, with a median of 153 g/dl. Median value of peripheral oxygen saturation at admission was 82.1% (range 44-99%), and 40 (22%) of them required oxygen support with a facial mask.

Table 1: Corticosteroids and Tocilizumab used during treatment.

Corticosteroids	**N (%)**
Dexamethason	155 (85.2)
Metilprednisolone	4 (2.2)
No therapy	23 (12.6)
Total	182 (100)
Tocilizumab	**N (%)**
No	166 (91.2)
Yes	16 (8.8)
Total	182 (100)

Table 2: Complication during hospital treatment.

Complication	**N (%)**
No	94 (51.6)
ARDS	84 (46.2)
PTE	4 (2.2)
Total	182 (100)

Total of 159 (87.4%) patients received corticosteroids during treatment, 155 (85.2%) Dexamethason in a dose of 6 mg per day for 10 days and 4 (2.2%) patients Metilprednizolon, in a dose of 80 mg per day, total 8 days. Tocilizumab in a dose of 600mg twice daily was given to 16 (8.8%) patients, while 166 (91.2%) did not receive it (Table 1). During treatment, 88 (48.4%) of patients developed one of the possible life-threatening complications: acute respiratory distress syndrome or pulmonary embolism (Table 2). Corticosteroids were used in total 159 (87.4%) patients, and 78 (48.4%) of them developed complications, while 81 (51.6%) did not (Table 3). Chi-square test did not find any difference between these groups.

Tocilizumab was used in total 16 (8.8%) patients, and 11 (6%) of them developed complications, while 5 (2.7%) did not (Table 3). Chi-square test did not find any difference between these groups. Among patients who used corticosteroids 94 (51.7%) of them survived, and 65 (35.7%) died (Table 4). Nine patients who received tocilizumab survived and seven died (Table 4). Chi-sqare test found no difference in outcome regarding use of corticosteroids and tocilizumab, $p>0.05$. We used univariate binary regression to determine possible influence of multiple factors (prehospital time, age, sex, presented complications, CRP values, use of tocilizumab and corticosteroids) to outcome of the disease. The statistically significant individual influence ($p<0.05$) according to Wald coefficients were: complications (Wald=19.19; OR= 0.09), age (Wald=6.76:=OR=1.07), and values of CRP (Wald=6.34; OR=1.006).

Table 3: Complications in a patients receiving corticosteroids and Tocilizumab.

		Corticosteroids Use		Total
		No (%)	Yes (%)	
Complications	No (%)	16 (8.8)	78 (42.8)	94 (51.6)
	Yes (%)	7 (3.8)	81 (44.6)	88 (48.4)
Total		23 (12.6)	159 (87.4)	182 (100)
		Tocilizumab Use		Total
		No (%)	Yes (%)	
Complications	No (%)	89 (48.9)	5 (2.7)	94 (51.6)
	Yes (%)	77 (42.3)	11 (6)	88 (48.4)
Total		166 (91.2)	16 (8.7)	182 (100)

Table 4: Outcome in patients receiving corticosteroids and tocilizumab.

	Corticosteroids use		Total
	No (%)	Yes (%)	
Survived, N (%)	22 (12.1%)	94 (51.7%)	116 (63.7%)
Died, N (%)	1 (0.5%)	65 (35.7%)	66 (36.2%)
Total	23 (12.6%)	159 (87.4%)	182 (100%)
	Tocilizumab Use		Total
	No (N. %)	Yes (%)	
Survived, N (%)	107 (58.8%)	9 (4.9%)	116 (63.7%)
Died, N (%)	59 (32.4%)	7 (3.9%)	66 (36.2%)
Total	166 (91.2%)	16 (8.8%)	182 (100%)

Other variables were not of significant influence. The values of Cox and Snell R^2=0.356 and Nagelkerke R^2=0.483 show that the set of variables explain 35.6% to 48.3% of the variance. Hosmer and Lemeshow test support the claim that the model is good: Chi-sqare =12.312, p=0.138.

DISCUSSION

The use of corticosteroids in the treatment of bacterial or viral infection is always controversial. Corticosteroids affect the innate and adaptive immune systems and can improve conditions in many infectious states, but also in some cases no improvement is achieved[8]. In some syndromes, like SARS, MERS or severe influenza, corticosteroids have been widely used, but without strong evidence of efficacy. On the other hand, some studies of corticosteroid use in SARS or MERS concluded that this therapy can also be harmful[9]. The recovery trial proved efficacy of using dexamethason (6 mg/day/10 days) but only in patients who required respiratory support. In these patients, corticosteroid therapy reduced 28-day overall mortality[10]. Cytokine storm is a usual manifestation of the severe form of COVID-19. The main characteristics are systemic inflammatory response and elevated levels of cytokines, including CRP, ferritin, interleukin-6. which usually lead to mutiple organ dysfunction[11,12]. Acute respiratory distress syndrome (ARDS) has been described in almost half of the COVID-19 patients who developed severe forms of the disease. Use of corticosteroids in such patients can improve clinical status and shorten the requirement for mechanical ventilation, with a reduction in mortality[13]. The use of corticosteroids in patients with moderate to severe ARDS is also recommended by The Society of Critical Care Medicine and European Society of Intensive Care Medicine[14]. So far, almost all studies conducted during COVID-19 pandemic suggest that corticosteroid therapy in COVID-19 must be titrated and tampered after clinical improvement. Also prolonged treatment or high dosage of corticosteroids should be avoided[15]. In our study almost 88% of the patients received corticosteroidal therapy. Despite that, 81 developed clinical presentation with complications, and 65 died, which is almost 41%. Acute respiratory distress syndrome was a complication presented in 84 (46.2%) cases which is similar to previously published studies[16]. Unfortunately, most of the patients arrived after 7 days of presented symptoms and treatment as outpatients, already with severe clinical presentation at admission, which in most cases progressed to non-invasive or invasive ventilation. Use of tocilizumab had different results in patients with Covid-19, which depended of disease severity, type of care and protocol used[17]. In most cases, the reason for use of tolicizumab was increase in CRP values, ferritin or dramatic deterioration of clinical state. Protocols for tolicizumab changed over the time, while in the beginning two doses of a maximum of 800 mg per dose were recommended, but after conducted studies the dose was set to one, and second dose only as optional[18].

Table 5: R^2 values : Cox and Snell/Nagelkerke.

Step	-2 Log likelihood	Cox & Snell R^2	Nagelkerke R^2
1	104.487[a]	0.356	0.483
Hosmer and Lemeshow test			
Step	Chi-square	df	Sig.
1	12.312	8	0.138

Table 6: Univariate binary logistic regression.

							95.0% C.I. for EXP (B)	
	B	S.E.	Wald	df	Sig.	OR	Lower	Upper
Tocilizumab use	0.932	0.925	1.015	1	0.314	2.538	0.415	15.542
Corticosteroids use	-2.054	1.175	3.057	1	0.080	0.128	0.013	1.282
Sex	-0.286	0.538	0.283	1	0.595	0.751	0.261	2.157
Age	0.070	0.027	6.763	1	0.009	1.072	1.017	1.130
Prehospital	0.131	0.076	2.976	1	0.084	1.140	0.982	1.323
CRP	0.006	0.002	6.347	1	0.012	1.006	1.001	1.011
Complications	-2.316	0.529	19.193	1	0.000	0.099	0.035	0.278
Constant	-6.437	2.187	8.665	1	0.003	0.002		

Results of the studies vary, from recommendation of use with significant improval and survival rates[19,20] to the opposite, where no positive influence to clinical course of COVID-19 disease has been observed, with even the possibility to deteriorate the outcome[21,22]. We also did not notice any significant improvement in patients who received tocilizumab, with or without corticosteroids. The main predictive factors for positive or unfavourable outcomes were age, values of CRP at admission, and developed complications during the treatment.

Limitation of the study

We were not able to follow values of C-reactive protein or Interleukin-6 during the treatment with corticosteroids and tocilizumab, since during the COVID-19 pandemic laboratories were under high pressure and could not receive and process so many requests for additional test. In that situation it is difficult to distinct influence of COVID itself, and concomitant cardivascular diseases for the clinical course. Nevertheless, out results are similar to the form previous studies: use of corticosteroids and tocilizumab are not "game-changers", especially in the patients with concomitant cardiovascular diseases.

CONCLUSIONS

The use of corticosteroids and tocilizumab in the treatment of COVID-19 patients with pneumonia remains controversial. Some studies have even shown that it may improve clinical presentation and prevent fatal outcomes; in most cases, there have been no significant results to confirm this hypothesis. Our results in patients with comorbid heart disease and COVID-19 pneumonia did not demonstrate that corticosteroids and tocilizumab can be effective in preventing complications or fatal outcomes.

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AUTHOR'S CONTRIBUTIONS

Osmani Z: methodology, investigation. **Paralija B:** critical review, data processing. **Baljić R:** review and editing, formal analysis. All authors reviewed and approved the final version of the article.

CONFLICT OF INTEREST

None to declare.

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