ORIGINAL ARTICLE

https://doi.org/10.1590/1806-9282.20210602

Tocilizumab is useful for coronavirus disease 2019 patients: the key point is timing

Muhammet Gülhan[1*], Uğur Önal[1], Neşe Demirci[1], Gulcan Cetin[2], Abdullah Calisir[3], Damla Köksalan[3], Kübra Solmaz[3], Ayhan Kars[4], Cetin Kilinc[5], Sedat Gülten[6]

SUMMARY

OBJECTIVE: In coronavirus disease 2019, a rapidly progressive inflammatory process is considered to be the main cause of organ damage and mortality. Therefore, the importance of anti-inflammatory treatments such as tocilizumab is increasing.

METHODS: A total of 107 patients who received tocilizumab between March 2020 and March 2021 were included in the study. The primary termination point was mortality. We compared surviving and deceased patients by the stage of the disease and where the drug was given (service or intensive care unit).

RESULTS: The mean age was 60.8±14.6 years (minimum 29 years, maximum 96 years). According to the WHO staging system, 16 (15%) patients had moderate, 47 (43.9%) patients had severe, 44 (41.1%) patients had a critical illness. Although all patients were admitted to the service, 26 (24.3%) patients received tocilizumab in the intensive care unit. Of 107 patients, 80 (74.7%) survived and 27 (25.2%) died. Mortality was found to be significantly higher in critical patients (96.3%), severe patients (3.7%), and moderate patients (0%) ($p<0.001$). Peripheral oxygen saturation measured at admission was found to be significantly lower in patients who died. The initial saturations ($p=0.008$) were found to have independent effects on mortality.

CONCLUSION: The results showed that tocilizumab is an effective treatment option for coronavirus disease 2019 disease and reduces mortality, but the key point is timing.

KEYWORDS: Tocilizumab. Early treatment. Mortality. Peripheral oxygen saturation monitoring.

INTRODUCTION

After cases of novel coronavirus [coronavirus disease 2019 (COVID-19)/severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)] pneumonia were reported in Wuhan City, Hubei Province, China, in December 2019, the World Health Organization (WHO) declared the outbreak as a "global pandemic" on March 11, 2020. The WHO reported 163,212,429 cases and 3,386,825 deaths until May 19, 2021[1].

At present, many antiviral agents have been tried for COVID-19, but none of them are sufficient and effective alone. Chloroquine and hydroxychloroquine have also been mainly used to treat COVID-19 infection, as they have been examined in the treatment of the previously seen SARS and Middle East Respiratory Syndrome (MERS) epidemic[2]. The lopinavir/ritonavir combination was used in the treatment of SARS and was also evaluated in the treatment of COVID-19[3]. Wang et al. used the combination of lopinavir/ritonavir, arbidol, and Shufeng Jiedu capsule in the treatment of COVID-19 and stated that this combination has some clinical benefits[4]. Favipiravir and Remdesivir are other drugs that are also used in the treatment of COVID-19. Some studies have shown that these drugs may have some advantages[5,6].

The occurrence of cytokine storm during COVID-19 infection is a hyperacute condition that causes mortality and needs to be prevented quickly. The cytokine storm, defined in the previous studies involving COVID-19 patients, has been better understood daily[7].

Due to the cytokine storm, which occurs during COVID-19 infection, alternative treatments are needed, which gradually increases the importance of anti-inflammatory drugs. It turned out that anti-inflammatory drugs are as important as antivirals. For this purpose, interleukin (IL)-1 receptor antagonists, (IL)-6

[1]Kastamonu Training and Research Hospital, Department of Infectious Diseases – Kastamonu, Turkey.
[2]Kastamonu Training and Research Hospital, Department of Chest Diseases – Kastamonu, Turkey.
[3]Kastamonu Training and Research Hospital, Department of Internal Medicine – Kastamonu, Turkey.
[4]Kastamonu Training and Research Hospital, Department of Ear, Nose and Throat Diseases – Kastamonu, Turkey.
[5]Kastamonu Training and Research Hospital, Department of Microbiology – Kastamonu, Turkey.
[6]Kastamonu Training and Research Hospital, Department of Biochemistry – Kastamonu, Turkey.
*Corresponding author: mustafammg@hotmail.com
Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 22, 2021. Accepted on July 12, 2021.

receptor antagonists, Janus kinase inhibitors, granulocyte-macrophage colony-stimulating factor, anti-tumor necrosis factor-α, and corticosteroids were used in the treatment of COVID-19[8].

Tocilizumab is the most studied anti-inflammatory agent for the treatment of COVID-19 infection. It has also been primarily considered in the treatment of severe COVID-19 pneumonia, which is thought to have high (IL)-6 levels and is accompanied by a cytokine storm. However, the results of tocilizumab treatment are controversial. While it was found to be beneficial in some studies, other studies reported that it is not effective[9,10].

In this study, we evaluated our patients who used tocilizumab. In this study, we investigated whether tocilizumab has an effect on mortality in COVID-19 infection and whether the time of administration of tocilizumab treatment has an effect on mortality.

METHODS

COVID-19 treatment decision was made following the guideline by The Turkish Ministry of Health. This guide was first published in May 2020 and updated over time. The last update was done on May 7, 2021[11]. According to this guide, treatment regimens changed (Table 1).

Study design

This study was primarily designed for patients who were followed in the pandemic service. Patients who were admitted to the pandemic service and received tocilizumab between March 2020 and March 2021 were included in the study. Patients who were admitted directly to the intensive care unit (ICU) on admission were excluded from the study. Patients under the age of 18 years were excluded from the study. Data were analyzed retrospectively.

Initial oxygen (O_2) saturations were recorded at admission. Peripheral O_2 saturation measured at admission was used to define the term "late admission." Daily blood tests were done. Patients were classified according to the WHO classification system[12].

The primary termination point was determined as mortality. We thought that timing was important for tocilizumab treatment. Therefore, we compared the stages of the disease in which patients had taken the drug.

Statistical analyses were performed with the SPSS-20.0 program (SPSS, Chicago, IL, USA). Numerical data were expressed as mean and standard deviation, whereas categorical data were expressed as percentages or proportions. The chi-square test was used to analyze categorical variables. Comparison between three groups for numeric variables was made using the one-way ANOVA test. Factors having an independent effect on mortality were evaluated by linear regression analysis. A p-value <0.05 was considered to be statistically significant.

Ethics committee approval was received from Bolu Izzet Baysal University.

Table 1. Turkey's ministry of health coronavirus disease 2019 guide antiviral treatment suggestions.

Treatments			
	First choice	Second choice	Third choice
First suggestion	Hydroxychloroquine+ Azithromycin+ Oseltamivir	Lopinavir/ Ritonavir	Favipiravir
Second suggestion	Hydroxychloroquine+ Azithromycin+ Oseltamivir	Lopinavir/ Ritonavir	
Third suggestion	Hydroxychloroquine Azithromycin	Favipiravir	
Final suggestion	Favipiravir		

RESULTS

A total of 107 patients were included in the study. The mean age was 60.8±14.6 years (minimum 29 years, maximum 96 years). According to the WHO staging system, 16 (15%) patients had moderate, 47 (43.9%) patients had severe, 44 (41.1%) patients had a critical illness.

Of 107 patients, 97 were PCR-positive and 10 were antibody-positive; 78.5% of the patients were males (84) and 21.5% were females (23). Despite all patients hospitalized to service on admission, 26 (24.3%) received tocilizumab in the ICU.

Of 107 patients, 80 (74.7%) survived and 27 (25.2%) died. A total of 15 (14%) patients from survivors were discharged with an oxygen concentrator. When compared to the patients who take the tocilizumab in the ICU COVID service, it was observed that the mortality rate was 8.6% in service and 76.9% in ICU patients (Figure 1). The difference was statistically significant (p<0.001).

While 76.5% of the patients recovered completely, 14.8% were discharged with oxygen and received tocilizumab in the service. In contrast, 11.5% of those recovered completely, and 11.5% were discharged with oxygen receiving tocilizumab in the ICU. While 8.6% of the patients who received tocilizumab in the service died, 76.9% who received it in the ICU died. The difference was statistically significant (p<0.001).

The relationship between the characteristics of the patients and mortality was also examined in the study. Mortality was significantly higher in critical (96.3%) patients than in severe (3.7%) and moderate (0%) patients (p<0.001). Mortality was significantly higher for males (88.9%) than females (11.1%) (p=0.042). Initial O_2 saturation was significantly lower in deceased patients (p<0.001).

Factors having an independent effect on mortality were evaluated by linear regression analysis (Table 2). Initial saturation, highest ferritin, and lowest lymphocyte values had independent effects on mortality.

DISCUSSION

A hyperacute inflammatory process is observed in the course of COVID-19 disease. This process has been named cytokine release syndrome and hyperinflammatory syndrome in the previous studies[9,13,14]. These conditions have been previously seen in various diseases such as some viral diseases, sepsis, rheumatological diseases, and after the use of some drugs. In addition, lymphopenia, high CRP, ferritin, triglyceride, lactate dehydrogenase (LDH), and D-dimer values seen in COVID-19 can also be seen in these syndromes[14,15]. As a result, uncontrolled and massive release of inflammatory cytokines is seen, and this abnormal rise can be measured[16].

An abnormal immune response occurs in COVID-19 infection. Hyperactivation of T cells and uncontrolled and unpreventable cytokine release are held responsible for the poor prognosis of diseases[17]. Studies on viral load in SARS patients have shown that the prognosis worsens even as the

Table 2. Factors having an independent effect on mortality.

	B	t	p
Age	0.010	1425	0.157
Hospitalization day	-0.009	-0.601	0.549
Initial O_2 saturation	-0.051	-2716	0.008
Highest CRP	0.002	0.938	0.351
Highest ferritin	0.001	2733	0.007
Lowest lymphocyte	-1110	-3856	0.000

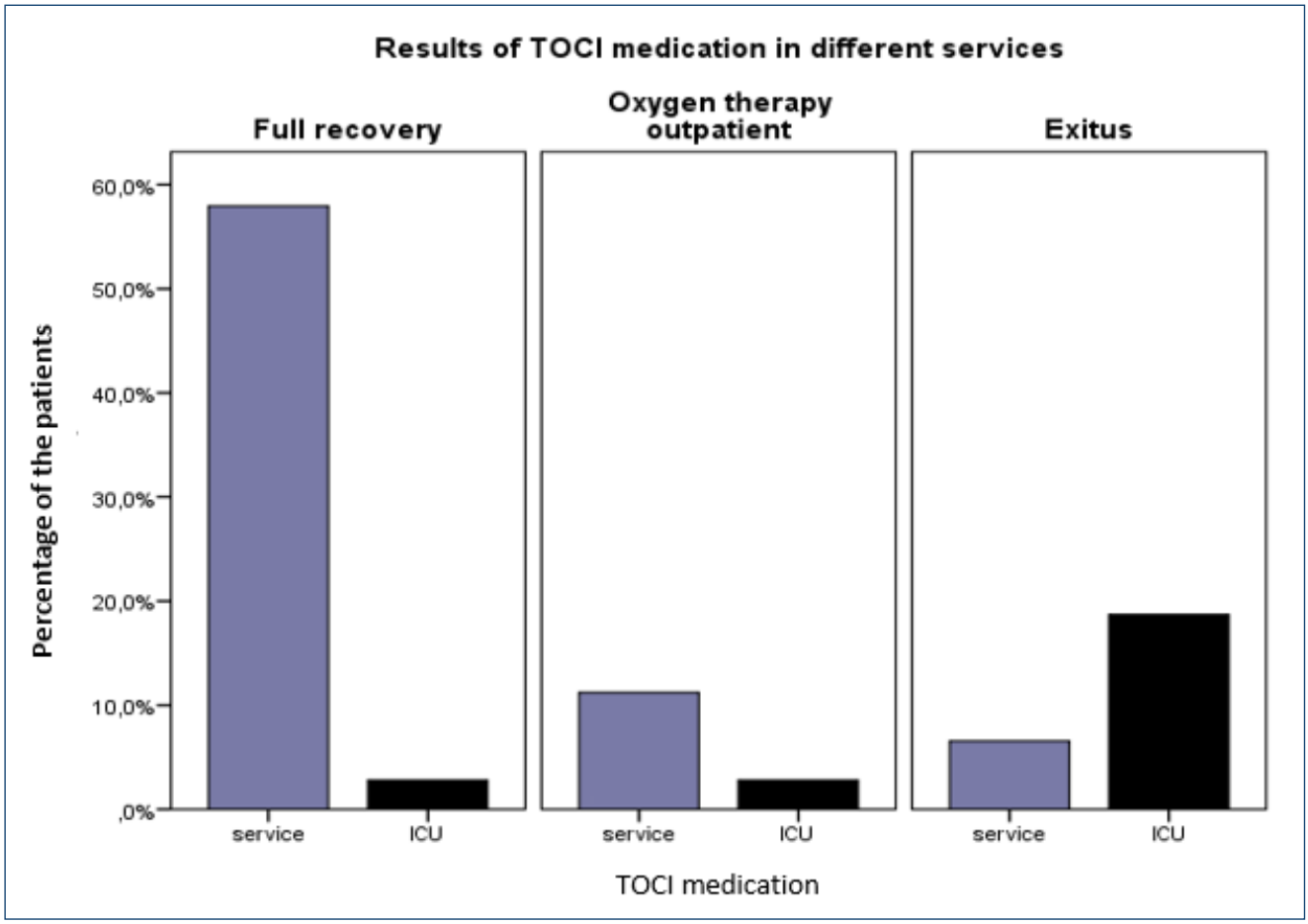

Figure 1. The comparison between ICU and service patients according to mortality, discharge from hospital with oxygen, and full recovery.

viral load of patients decreases due to high inflammation. These results suggest that anti-inflammatory therapy is more critical than antivirals[14].

Coronavirus infections had high expression of IL-6, including COVID-19, SARS-CoV, and MERS-CoV. IL-6 plays an important role in acute inflammation. It regulates acute inflammation. However, excessive IL-6 signaling leads to organ damage[14,15].

IL-6 inhibitor (tocilizumab) is recommended for anti-inflammation in COVID-19 patients. However, some of these studies recommend tocilizumab only for severely or critically ill patients[14,15]. Luo et al. used tocilizumab in 15 patients and stated that CRP values are decreased in all patients. Although seven of them were critically ill, they reported that only three patients died[7]. Xu et al. administered tocilizumab to 21 patients and reported that all patients survived[18]. In our study, the rate of COVID-19 cases with severe and critical diseases was over 40%, while 15%. All of these cases were treated with tocilizumab in the service or ICU. Unlike the studies above, anti-inflammatory treatment (tocilizumab) was applied to the moderate COVID-19 patients.

Klopfenstein et al. compared two groups, one taking standard therapy and the other traditional therapy with tocilizumab drug. They pointed out that in common therapy, group mortality and ICU admission are significantly higher[19]. Conversely, Colaneri et al. showed that tocilizumab did not affect ICU admission substantially or 7-day mortality[20]. Studies done in ICU patients have poorer outcomes. In their study conducted with 65 patients, Campochiaro et al. administered tocilizumab to 32 of them and compared the two groups. They found no significant difference when comparing mortality and clinical outcomes. However, all of the patients included in the study were patients who needed high-flow oxygen or noninvasive ventilation[21].

Gorgolas et al. similarly demonstrated that tocilizumab is beneficial in early administration[22]. In this study, when comparing the patients who took the tocilizumab in COVID service with those who took it in the ICU, it was observed that the mortality rate was 8.6% in service and 76.9% in ICU patients. The difference was statistically significant ($p<0.001$). It was noted that 26 of 27 patients who were died were critically ill. Only one of them was severe. Mortality was significantly higher in critical (96.3%) patients than in severe (3.7%) and moderate (0%) patients ($p<0.001$). We compared the deceased and survived patients according to initial O_2saturation. Initial O_2 saturation was significantly lower in deceased patients. Using linear regression analysis, it was observed that initial O_2 saturation, highest ferritin, and lowest lymphocyte values had independent effects on mortality.

Previous studies have shown that patients can benefit from tocilizumab even if they are treated in the ICU[23]. Although we recommend early treatment, we believe that every patient can receive tocilizumab. In our study, the fact that 76.9% of the patients given tocilizumab in the ICU passed away supports our argument that "the sooner, the better." It will be wiser to provide some patients with unnecessary treatment rather than expose them to mortal risk since we are not sure who will go worse.

For this reason, we suggest that the best approach is not to allow patients to progress, by starting anti-inflammatory therapy as soon as signs of inflammation appear. In studies related to this, tocilizumab was recommended for patients with CRP ≥75 mg/L and saturation <92%[24]. We suggest that even these values may be insufficient. We recommend tocilizumab for patients with a CRP greater than 50 mg/L and/or a peripheral O_2 saturation of less than 93. However, it should be kept in mind that some patients progress very rapidly. In this case, we suggest that the decision of the expert who follows up the patient is the most crucial criterion. We recommend that for patients with locally determined insufficient prognosis criteria, tocilizumab treatment can be started without waiting for these values to occur.

In addition, in our study, we showed that low peripheral O_2 saturation has an independent effect on mortality. We suggest that it would be beneficial to monitor the peripheral O_2 saturation at home by the patients themselves to prevent the late arrival of patients who are followed up or treated at home.

CONCLUSIONS

There is still no antiviral therapy that affects mortality. However, anti-inflammatory treatments affect mortality. It can be revealed that anti-inflammatory treatment is more important than antivirals; our study showed that early use of tocilizumab reduces mortality.

To reduce mortality, two simple steps are needed: (1) Monitoring peripheral O_2 saturation at home to avoid late hospitalization. (2) Tocilizumab treatment should be given before the cytokine storm occurs.

ACKNOWLEDGMENTS

We would like to thank Prof. Dr. Peri Arbak for her contributions.

AUTHORS' CONTRIBUTIONS

MG: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original

draft, Writing – review & editing. **UÖ:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization. **ND:** Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **GC:** Investigation, Methodology, Writing – original draft, Writing – review & editing. **AC:** Conceptualization, Data curation, Writing – review & editing. **DK:** Conceptualization, Data curation. **KS:** Conceptualization, Data curation. **AK:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **CK:** Conceptualization, Investigation, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **SG:** Conceptualization, Data curation.

REFERENCES

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. [cited on 2021 May 19]. Available from: https://covid19.who.int/.
2. Shukla AM, Archibald LK, Wagle Shukla A, Mehta HJ, Cherabuddi K. Chloroquine and hydroxychloroquine in the context of COVID-19. Drugs Context. 2020;9:2020-4-5. https://doi.org/10.7573/dic.2020-4-5
3. Chu CM, Cheng VCC, Hung IFN, Wong MML, Chan KH, Chan KS, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. Thorax. 2004;59(3):252-6. https://doi.org/10.1136/thorax.2003.012658
4. Wang Z, Chen X, Lu Y, Chen F, Zhang W. Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment. Biosci Trends. 2020;14(1):64-8. https://doi.org/10.5582/bst.2020.01030
5. Ghasemnejad-Berenji M, Pashapour S. Favipiravir and COVID-19: a simplified summary. Drug Res (Stuttg). 2021;71(3):166-70. https://doi.org/10.1055/a-1296-7935
6. Davies M, Osborne V, Lane S, Roy D, Dhanda S, Evans A, et al. Remdesivir in treatment of COVID-19: a systematic benefit-risk assessment. Drug Saf. 2020;43(7):645-56. https://doi.org/10.1007/s40264-020-00952-1
7. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. J Med Virol. 2020;92(7):814-8. https://doi.org/10.1002/jmv.25801
8. Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmaco-immunomodulatory therapy in COVID-19. Drugs. 2020;80(13):1267-92. https://doi.org/10.1007/s40265-020-01367-z
9. Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. Autoimmun Rev. 2020;19(7):102568. https://doi.org/10.1016/j.autrev.2020.102568
10. Salvarani C, Dolci G, Massari M, Merlo DF, Cavuto S, Savoldi L, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. JAMA Intern Med. 2021;181(1):24-31. https://doi.org/10.1001/jamainternmed.2020.6615
11. https://covid19.saglik.gov.tr/Eklenti/40719/0/covid19rehberieriskinhastayonetimiveted avipdf.pdf [cited on 2021 May 19].
12. World Health Organization. Coronavirus disease (COVID-19) technical guidance: Patient management. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management. Accessed March 4, 2020.
13. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmun Rev. 2020;19(6):102537. https://doi.org/10.1016/j.autrev.2020.102537
14. Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun. 2020;111:102452. https://doi.org/10.1016/j.jaut.2020.102452
15. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020;55(5):105954. https://doi.org/10.1016/j.ijantimicag.2020.105954
16. Kotch C, Barrett D, Teachey DT. Tocilizumab for the treatment of chimeric antigen receptor T cell-induced cytokine release syndrome. Expert Rev Clin Immunol. 2019;15(8):813-22. https://doi.org/10.1080/1744666X.2019.1629904
17. Rodríguez Y, Novelli L, Rojas M, De Santis M, Acosta-Ampudia Y, Monsalve DM, et al. Autoinflammatory and autoimmune conditions at the crossroad of COVID-19. J Autoimmun. 2020;114:102506. https://doi.org/10.1016/j.jaut.2020.102506
18. Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA. 2020;117(20):10970-5. https://doi.org/10.1073/pnas.2005615117
19. Klopfenstein T, Zayet S, Lohse A, Balblanc JC, Badie J, Royer PY, et al. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. Med Mal Infect. 2020;50(5):397-400. https://doi.org/10.1016/j.medmal.2020.05.001
20. Colaneri M, Bogliolo L, Valsecchi P, Sacchi P, Zuccaro V, Brandolino F, et al. Tocilizumab for treatment of severe COVID-19 patients: preliminary results from SMAtteo COvid19 REgistry (SMACORE). Microorganisms. 2020;8(5):695. https://doi.org/10.3390/microorganisms8050695
21. Campochiaro C, Della-Torre E, Cavalli G, Luca G, Ripa M, Boffini N, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. Eur J Intern Med. 2020;76:43-9. https://doi.org/10.1016/j.ejim.2020.05.021
22. Górgolas Hernández-Mora M, Cabello Úbeda A, Prieto-Pérez L, Villar Álvarez F, Álvarez Álvarez B, Rodríguez Nieto, et al. Compassionate use of tocilizumab in severe SARS-CoV2 pneumonia. When late administration is too late. medRxiv. 2020.06.13.20130088. https://doi.org/10.1101/2020.06.13.20130088
23. Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, et al. Association between early treatment with tocilizumab and mortality among critically Ill patients with COVID-19. JAMA Intern Med. 2021;181(1):41-51. https://doi.org/10.1001/jamainternmed.2020.6252
24. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637-45. https://doi.org/10.1016/S0140-6736(21)00676-0