ACQUAINT PUBLICATIONS ....Disseminate your Research

Journal of Medical Case Reports and Case Series ISSN: 2692-9880

Case Report Volume 3 Issue 12

Is Tocilizumab a game-changer in managing severe COVID-19? A case report from Ile-Ife, Nigeria.

Tajudin Adesegun Adetunji, MBBS, FWACP[1*], Ahmad Abefe Sanusi, MBChB, MWACP[1], Uchenna Chidi Eke, MBBS, MWACP[1], Ahmed Omokayode Idowu, MBChB, MWACP[1], Olusola Fajobi, MBChB, FWACP[2], Ummulkhair Funke Adetunji, MBChB[3], Temitope Olumuyiwa Ojo, MBChB, FMCPH[4]

[1]Department of Medicine, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria.

[2]Department of Community Health, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria

[3]Department of Ophthalmology, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife

[4]Department of Community Health, Obafemi Awolowo University and Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria

[*]**Corresponding Author:** Tajudin Adesegun Adetunji, MBBS, FWACP, Department of Medicine, Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria.

Received date: 24 June 2022; **Accepted date:** 12 August 2022; **Published date:** 12 September 2022

Citation: Adetunji TA, Sanusi AA, Eke UC, Idowu AO, Fajobi O, et al. (2022) Is Tocilizumab a game-changer in managing severe COVID-19? A case report from Ile-Ife, Nigeria. J Med Case Rep Case Series 3(12): https://doi.org/10.38207/JMCRCS/2022/DEC03120489

Abstract

Background: The coronavirus disease 2019 (COVID-19) outbreak, which began in December 2019, has expanded swiftly over the world, posing a serious health threat. Tocilizumab, an interleukin-6 monoclonal receptor antibody, has been used with cautious optimism in some institutions in the developed world to reduce the inflammatory response seen in severe COVID-19 patients. Its use in our clime is fraught with huge costs, limited experience, and non-availability.

Case Report: We report a 52-year-old Nigerian woman known diabetic who presented with a two-week history of high-grade with chills and rigors, headache, and lethargy. She subsequently developed a cough productive of scanty whitish sputum. There was a history of dysgeusia but no anosmia. Clinical status progressively worsened with breathlessness, hypoxemia and persistent desaturation, . Blood tests results showed markedly high C-reactive protein (CRP), elevated liver enzymes, and hyperglycemia. She received high-dose oxygen supplementation, systemic dexamethasone, insulin, and low molecular weight heparin in the early days of admission with only a marginal improvement in saturation. However, treatment was intensified with intravenous Tocilizumab on the fifth day of admission with dramatic improvement in oxygen saturation, and clinical statuswith a sharp and sustained drop in CRP. She was subsequently discharged home after sixteen days on admission.

Conclusion: Our patient had severe COVID-19 with markers of cytokine storm and metabolic derangements. However, the administration of Tocilizumab appears to have produced a dramatic improvement in the patient's recovery. The use of Tocilizumab is encouraged for severe COVID-19 cases as it may potentially improve the clinical outcome.

Keywords: COVID-19, SARS-CoV-2, C-reactive Protein, Cytokine storm, desaturation

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic has become a hydra-headed global health problem overwhelming the health systems of low and high-income countries alike. **[1]** The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of the disease, was first identified in December 2019 in the city of Wuhan, located in central China. **[2]** Nigeria quickly joined the league of affected countries with the first case reported on 27th February 2020. **[3]** As of March 17th, 2022, more than 255,000 Nigerians have been infected with COVID- 19 and approximately 3,142 have died. **[4]** Several measures have been instituted by the Federal Government of Nigeria through the Presidential Task Force on COVID-19 (PTF-COVID-19) together with the Federal and State Ministries of Health to curtail the spread of the disease and protect the health of Nigerians. Some of these measures have profoundly changed the lifestyles of the Nigerian populace. **[5]**

Although only a small percentage of COVID-19 patients experience severe symptoms that would necessitate hospitalization **[6]**, those who do have limited treatment options. There is currently no widely accepted standard of treatment, and new approaches are still being developed. **[7]** Patients with severe symptoms requiring hospitalization and even intensive care unit have been found to have a significant increase in inflammatory cytokines, especially interleukin 6. **[8]** Tocilizumab, an anti-IL-6 receptor monoclonal antibody, has been proposed as a

therapy for controlling the cytokine storm linked to severe COVID-19. Despite this, many centers in Nigeria have limited experience with this novel therapy for reasons of unavailability and the huge cost required.

This article presents a case of severe SARS-CoV-2 infection in a middle-aged patient with poorly controlled diabetes who had a trial of intravenous tocilizumab in addition to a short course of steroid, high dose supplemental oxygen, anticoagulant, and insulin with a favorable outcome.

Case Report

A 52-year-old Nigerian woman school proprietress was referred from a private facility in a neighboring state, having been managed for a febrile illness for 3 days without improvement despite completing a course of drugs. She presented with a two-week history of high-grade intermittent fever with associated chills and rigors, generalized headache, anorexia, and lethargy.

About one week later, she developed a cough, initially dry but later became productive of a scanty amount of whitish sputum. There was a positive history of dysgeusia but no anosmia. Four days later, breathlessness ensued with associated pleuritic chest pain. There was a positive history of prolonged close contact with a suspected case ofCOVID-19 at work. The suspected case had mild but similar symptoms but was not confirmed by testing. No history of altered sensorium, abdominal symptoms, lower urinary tract symptoms, reduction in urine volume, or bleeding tendencies. No history of prior COVID-19 vaccination.

She was diagnosed with diabetes 5 years earlier and was being managed with Metformin 1g twice daily and Gliclazide 60mg daily orally with poor glycaemic control. There was no history suggestive of any specific macrovascular or microvascular complications of diabetes. She did not smoke cigarettes or take alcohol.

Examination findings at presentation revealed a middle-aged woman, acutely ill-looking, in respiratory distress, lethargic, febrile (axillary temperature of 38°C), not pale, anicteric, cyanosed, dehydrated, and no pedal edema. She was tachypnoeic with a respiratory rate of 36cycles per min, oxygen saturation in room air was 85 %, and had coarse crepitations on the right lower lung zone. Her pulse rate was 120bpm and her blood pressure was 140/70mmHg with normal heart sounds. She had central obesity with hepatomegaly but the neurological examination was grossly normal.

A COVID-19 RDT antigen (COVID-19 Ag Rapid Test Device, LOT G2103022F, Abbott Rapid Diagnostics, Germany) as well as COVID-19 SARS CoV2 PCR tests done at presentation were positive (CT values: RdRp gene = 27.49, E-gene = 24.87, N-gene = 24.45). Her random blood glucose at presentation was 13mmol/L. The complete blood count result revealed a packed cell volume of 36 %, white cell count of cells per mm3 with neutrophils of 72 % and lymphocytes of 28 %, and platelets count of 206,000 per mm3. The serum electrolyte, urea and creatinine were creatinine - 66umol/l, chloride - 94mmol/l, potassium - 3.8mmol/l and sodium - 128mmol/l (low). The liver enzyme alanine transaminase was also elevated ALT – 108 IU/L (< 32). All serologic tests for HIV, HCV, and HBsAg came back negative. The C-reactive protein was significantly elevated >300mg/L (<10) **(Table 1).**

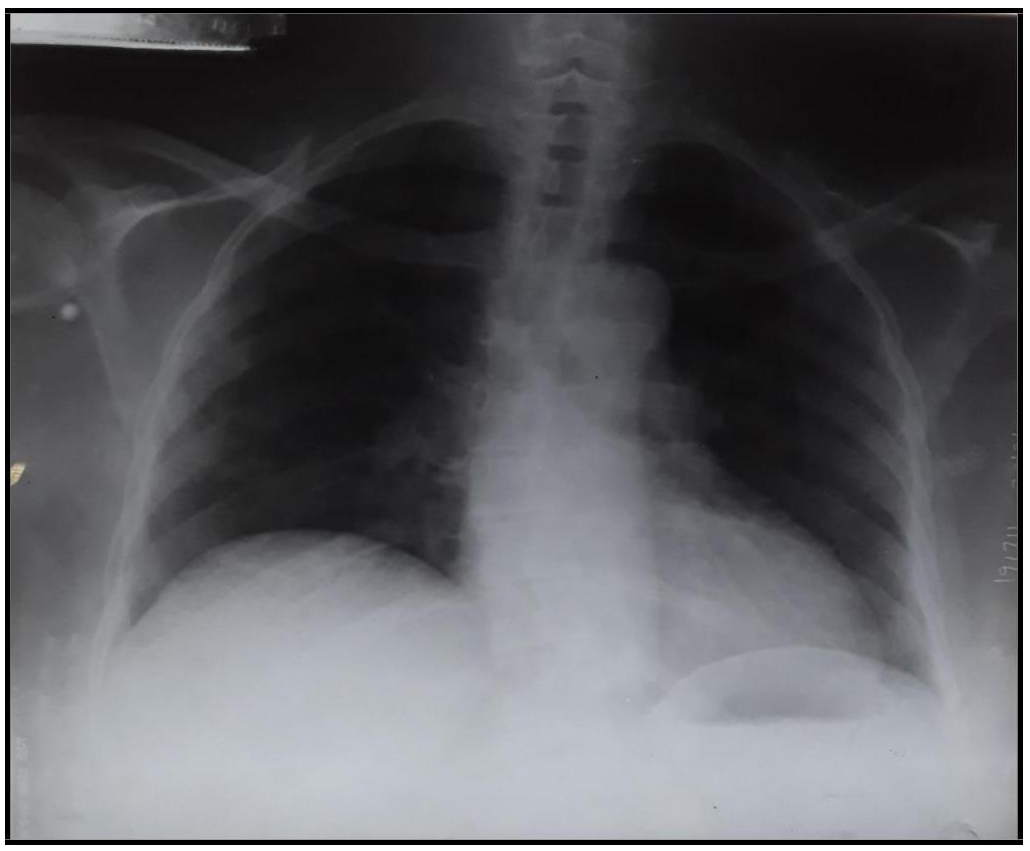
Table 1: Notable laboratory studies at baseline, during admission and at discharge

Parameters	**Value on admission**	**Value at Discharge (Day 15)**
Complete blood count (reference range)		
Packed cell volume (37 % to 47 %)	36 %	NR
White cell count (2,000 to 9,000 per mm^3)	6,300 per mm^3	,,
Neutrophil (40 % to 60 %)	72 %	,,
Lymphocyte (20 to 30 %)	28 %	,,
Platelets (90,000 to 150,000 per mm^3)	206,000 per mm^3	,,
C-reactive protein (CRP <10 mg/L)		
On admission:	> 300mg/L	2.84mg/L
Admission day 5 (48hrs post Tocilizumab)	20.6mg/L	
Serum electrolyte, urea and creatinine		
Sodium (135 to 150mmol/L)	128 mmol/L	135 mmol/L
Potassium (3.5 to 5.0mmol/L)	3.8 mmol/L	4.5 mmol/L
Chloride (96 to 110mmol/L)	94 mmol/L	104 mmol/L
Urea (2.5 to 5.8mmol/L)	NA	2.1 mmol/L
Creatinine (50 to 132µmol/L)	66 µmol/L	42 µmol/L

Liver function test		
Alanine transaminase (<32)	108 IU/L	80 IU/L
Alkaline phosphate (35 – 104 IU/L)	73 IU/L	59 IU/L (35 – 104)
Total bilirubin (up to 20µmol/L)	6 µmol/L	6 µmol/L
Conjugated bilirubin (up to 5µmol/L)	2 µmol/L	2 µmol/L
Viral serologies		
HIV	negative	
HBsAg	negative	
Anti-HCV	negative	

NR – Not repeated; () – reference range; NA – Not available.

Figure 1: Chest radiograph image on discharge



Note: Anterioposterior Chest radiograph showing aortic unfolding and cardiomegaly

An assessment of moderately severe SARS-COV-2 infection with hyperglycaemia on the background of Type 2 diabetes mellitus was made. She was commenced on supplemental oxygen by face mask at 6L/min, intravenous dexamethasone 6mg daily, intravenous augmentin 1.2g 12hourly, tab azithromycin 500mg daily PO for 3 days, tab vitamin C 1g daily PO, tab vitamin E 800units daily PO, tab zinc sulfate 20mg daily PO, subcutaneous glargine 10units nocte, intravenous fluid 0.9% normal saline 1litre 8hourly. Oxygen saturation and other vital signs were closely monitored.

Over the next 48hours, the clinical condition worsened with a progressive decline in oxygen saturation to 80-84 %, and supplemental oxygen was thus increased to 10litres per min. Hyperglycaemia also worsened with a peak prandial blood glucose rising to 19.2mmol/l. Pre-meal soluble insulin was introduced at 8 units thrice daily and subcutaneous glargine was increased to 14 units nocte. Vitals signs remained deranged with persistent pyrexia (Temperature > 38°c) tachycardia (Pulse rate >110b/mins) and tachypnoea (respiratory rate > 32cycles/min).

On the third day of admission, the patient complained of worsening fatigue, chest tightness, oxygen saturation worsened to 70-78 % on supplemental oxygen and glycemic control further worsened with a fasting blood glucose of 16.1mmol/l. Her blood pressure rose to a value of 154/89 mmHg and she was commenced on tab amlodipine 5mg daily PO, hydrochlorothiazide 12.5mg daily PO, and subcutaneous enoxaparin 40mg daily was added. The soluble insulin dose was increased to 20 units thrice daily, the oxygen flow rate was increased to 12litres per minute and the face mask was changed to a non-rebreather mask.

On the fourth day of admission, oxygen desaturation failed to improve despite a high dose of supplemental oxygen delivered via the non-rebreather mask. Non-invasive positive-pressure ventilation (NIPPV) was instituted but did not improve the oxygen saturation. At the same time, IV Tocilizumab was considered in addition to standard therapy. The patient and relatives were informed and appropriately counseled on this line of treatment. Meanwhile, the high dose of oxygen was further increased to a flow rate of 15litres per min via a non-rebreather mask. The following day, intravenous tocilizumab was procured and administered at a dose of 600mg in 150ml of normal saline over 90minutes. No signs of anaphylaxis were observed.

About 24hrs following administration of intravenous tocilizumab, the oxygen saturation increased steadily to 92 % on supplemental oxygen, and glycemic control improved with a fasting blood glucose down to 9.8mmol/L. The patient continued to make sustained clinical improvement as oxygen saturation increased to 95 % on supplemental oxygen and fasting blood glucose became 7.5mmol/l by the following morning. Dexamethasone was discontinued and repeat C-reactive protein reduced remarkably to 20.6mg/L within 72hrs. Blood pressure and other vitals became normalized and the oxygen flow rate was gradually reduced to 6-8L/min.

By the sixteenth day of admission, the patient had improved clinically and was weaned off supplemental oxygen and saturation level remained between 95 % - 99 % in room air. The C-reactive protein had normalized to 2.84mg/L (< 10), the SARS CoV2 PCR test was negative and the patient was successfully discharged on antihypertensives, metformin, linagliptin, and pre-mixed insulin.

Discussion

Tocilizumab has been recommended as a treatment strategy to control cytokine storms associated with COVID-19 infection. **[9,10]** Tocilizumab is a US Food and Drug Administration-approved humanised monoclonal antibody against the IL-6 receptor that is commonly used to treat CRS in the setting of chimeric antigen receptor T-cell therapy in hematologic patients. **[11]** It received U.S. FDA emergency use authorization (EUA) on June 24th, 2021, for the treatment of hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). **[12]** The data supporting this EUA are based on four clinical trials. These included one randomized, controlled, open-label, platform trial [Randomised Evaluation of COVID-19 Therapy (RECOVERY)] and three randomized, double-blind, placebo-controlled trials (EMPACTA, COVACTA, and REMDACTA). While all four clinical trials contribute to the FDA's understanding of Tocilizumab for the treatment of COVID-19, the most important scientific evidence on the potential benefit of Tocilizumab for its authorized use came from the RECOVERY and EMPACTA trials. **[13–15]** In Nigeria, however, intravenous and subcutaneous tocilizumab, approved for Rheumatoid arthritis and similar conditions may be used for severe COVID-19 with the clinical judgment of the physicians and in the setting of clinical trials with due approvals of the National Agency for Food and Drug Administration and Control (NAFDAC).

In this report, we present an obese hypertensive and diabetic woman who had clinical and laboratory indications of significant inflammation consistent with cytokine release syndrome due to severe COVID-19. She however responded to intravenous tocilizumab with a favorable clinical outcome along with rapid improvement in C-reactive protein (CRP) and glycemic control.

These findings are in keeping with reports of Guaraldi G. et al., and Luo P. et al., where a remarkable decline in inflammatory markers was observed after administering Tocilizumab to severe COVID-19 cases. **[16,17]**

We used CRP as a surrogate inflammatory marker since it has been widely accepted and we did not also have the resources to measure interleukin 6 (IL-6) levels. Our patient had markedly high initial CRP levels with a remarkable decline within 72hrs of tocilizumab administration.

Importantly, our patient was given a single dose of tocilizumab which improved her clinical outcome consistent with the study by Moes et al. which revealed that fixed dosing of tocilizumab at a dosage of 600mg is safe, logistically attractive, and cost-effective. **[18]** However, some studies have recommended repeated use of tocilizumab for severe COVID-19 infection to ensure a positive clinical outcome. **[17,19]** It is not known if this would apply to every clinical situation given the cost, unavailability, and regulatory requirement for the use of this medication in some countries.

A recent study revealed that the risk of in-hospital mortality among critically ill patients with COVID-19 infection was lower in patients treated with tocilizumab in the first 2 days of admission compared with patients whose treatment did not include early use of Tocilizumab. **[20]** Although our patient received the medication on the 5th day of admission due to the logistics of our practice environment, the clinical outcome was good. Furthermore, the use of tocilizumab reduces the length of hospital stay, and the need for intensive care and ventilatory support and thus improves mortality rate as demonstrated by the index case. **[21]**

To the best of our knowledge, we have described one of the first reported successful treatments of severe COVID-19 infection and concomitant cytokine release syndrome with tocilizumab in Nigeria.

Conclusion

The present case report demonstrates a clear temporal relationship between tocilizumab administration and rapid clinical improvement in a COVID-19 patient with a marked hyperinflammatory state. Although other concomitant therapies such as dexamethasone and oxygen supplementation were contributory, they would not obviate the need for tocilizumab given the rapid improvement that followed its use in our patient. Given the obvious limitations of these clinical observations, there is a need for more randomized controlled trials toevaluate the effects of tocilizumab on clinical outcomes in patients with severe SARS-CoV-2 infection and evidence of systemic inflammation, especially in a resource-limited setting like Nigeria.

Conflict of Interest: No conflict of interest exists

Abbreviations:

CRP - C-reactive protein

CRS - Cytokine release syndrome

ECMO - Extracorporeal membrane oxygenation

EUA - Emergency use authorization

Author's Contributions

Tajudin Adesegun Adetunji

Substantial contributions to conception and design, Acquisition of data, Analysis, and interpretation of data, Drafting the article, revising it critically for important intellectual content, Final approval of the version to be published

Ahmad Abefe Sanusi

Substantial contributions to conception and design, Acquisition of data, Analysis, and interpretation of data, Drafting the article, revising it critically for important intellectual content, Final approval of the version to be published

Uchenna Chidi Eke

Substantial contributions to conception and design, Acquisition of data, Analysis, and interpretation of data, Drafting the article, revising it critically for important intellectual content, Final approval of the version to be published

Ahmed Omokayode Idowu

Substantial contributions to conception and design, Acquisition of data, Analysis, and interpretation of data, Drafting the article, revising it critically for important intellectual content, Final approval of the version to be published

Olusola Fajobi

Substantial contributions to conception and design, Acquisition of data, Analysis, and interpretation of data, Drafting the article, revising it critically for important intellectual content, Final approval of the version to be published

Ummulkhair Funke Adetunji

Substantial contributions to conception and design, Acquisition of data, Analysis, and interpretation of data, Drafting the article, revising it critically for important intellectual content, Final approval of the version to be published

Temitope Olumuyiwa Ojo

Substantial contributions to conception and design, Acquisition of data, Analysis, and interpretation of data, Drafting the article, revising it critically for important intellectual content, Final approval of the version to be published

References

1. Amzat J, Aminu K, Kolo VI, Akinyele AA, Ogundairo JA, et al. (2020) Coronavirus outbreak in Nigeria: Burden and socio-medical response during the first 100 days. Int J Infect Dis. 98: 218-224.
2. World Health Organization. Covid-19 Situation Report. World Health Organ. 2020.
3. First Case of Corona Virus Disease Confirmed in Nigeria [Internet]. Ncdc.gov.ng. 2020.
4. Nigeria COVID - Coronavirus Statistics - Worldometer [Internet]. Worldometers.info. 2022.
5. NCDC Coronavirus COVID-19 Microsite [Internet]. Covid19.ncdc.gov.ng. 2022.
6. Menachemi N, Dixon BE, Wools-Kaloustian KK, Yiannoutsos CT, Halverson PK (2021) How Many SARS-CoV-2-Infected People Require Hospitalization? Using Random Sample Testing to Better Inform Preparedness Efforts. J Public Health Manag Pract. 27(3): 246-250.
7. Florindo HF, Kleiner R, Vaskovich-Koubi D, Acúrcio RC, Carreira B, et al. (2020) Immune-mediated approaches against COVID-19. Nat Nanotechnol. 15(8): 630-645.
8. Huang C, Wang Y, Li X, Ren L, Zhao J, et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 395(10223): 497-506.
9. Zhang S, Li L, Shen A, Chen Y, Qi Z (2020) Rational Use of Tocilizumab in the Treatment of Novel Coronavirus Pneumonia. Clin Drug Investig. 40(6): 511-518.
10. Kulanthaivel S, Kaliberdenko VB, Balasundaram K, Shterenshis MV, Scarpellini E, et al. (2021) Tocilizumab in SARS-CoV-2 Patients with the Syndrome of Cytokine Storm: A Narrative Review. Rev Recent Clin Trials. 16(2): 138-145.
11. Frey N, Porter D (2019) Cytokine Release Syndrome with Chimeric Antigen Receptor T Cell Therapy. Biol Blood Marrow Transplant. 25(4): e123-e127.
12. The Foods and Drugs Administration (2021) Coronavirus (COVID-19) Update: FDA Authorizes Drug for Treatment of COVID-19. Fda.
13. RECOVERY Collaborative Group. (2021) Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 397(10285): 1637-1645.
14. McCreary EK, Meyer NJ (2021) Covid-19 controversies: the tocilizumab chapter. BMJ. 372: n244.
15. Salama C, Han J, Yau L, Reiss WG, Kramer B, et al. (2021) Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 384(1): 20-30.
16. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, et al. (2020) Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol. 2(8): e474-e484.
17. Luo P, Liu Y, Qiu L, Liu X, Liu D, et al. (2020) Tocilizumab treatment in COVID-19: A single center experience. J Med Virol. 92(7): 814-818.
18. Moes DJAR, van Westerloo DJ, Arend SM, Swen JJ, de Vries A,

et al. (2022) Towards Fixed Dosing of Tocilizumab in ICU-Admitted COVID-19 Patients: Results of an Observational Population Pharmacokinetic and Descriptive Pharmacodynamic Study. Clin Pharmacokinet. 61(2): 231-247.

19. Vu CA, DeRonde KJ, Vega AD, Maxam M, Holt G, et al. (2020) Effects of Tocilizumab in COVID-19 patients: a cohort study. BMC Infect Dis. 20(1): 964.
20. Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, et al. (2021) Association Between Early Treatment with Tocilizumab and Mortality Among Critically Ill Patients With COVID-19. JAMA Intern Med. 181(1): 41-51.
21. Sarhan RM, Madney YM, Abou Warda AE, Boshra MS (2021) Therapeutic efficacy, mechanical ventilation, length of hospital stay, and mortality rate in severe COVID-19 patients treated with tocilizumab. Int J Clin Pract. 75(6): e14079.