Retrospective Observational Analysis of Tocilizumab Outcomes in COVID-19 Patients at a Tertiary Care Hospital

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Abstract

Background: Tocilizumab (TCZ), a monoclonal antibody against interleukin-6 (IL-6), was recommended for treatment of Covid-19 patients with a risk of cytokine storm but showed variable effect on outcome. The aim was to assess the association of outcome following tocilizumab administration with various physiological, pathological and pharmacological factor in Covid- 19 patients.

Methods: Retrospective observational study from June 2020 to July 2020. All indoor Covid positive patients who received tocilizumab were included and relevant information was captured in the case record form. Data was analyzed to the study association of various physiological factors, comorbidities, severity of disease, laboratory parameters and co-administered drugs with the outcome following tocilizumab administration.

Results: Total 25 patients received tocilizumab during study period. Older age group (p=0.001), high NEWS score, hypertension (OR: 3.62; p=0.05) and hydroxychloroquine(HCQ) administration (OP=6.66; p=0.009) showed significant association with a worst outcome. Hypertension and hydroxychloroquine usage was analyzed after adjustment with NEWS score using MH adjusted analysis, which revealed a trend of worst outcome in HCQ recipients but the association was not significant with hypertension. High pre-treatment IL-6 (death 570.11+498.76; discharge110.31+ 49.68; p: 0.0011); high post-treatment ferritin level (death 1756.5+ 1622.03; discharge 711.71+ 421.23; p: 0.019) as well as post-tocilizumab rise in ferritin level was associated with worst outcome (p= 0.029).

Conclusion: Participants having higher cytokine level/or high NEWS score were unlikely to benefit from tocilizumab. Increased in ferritin level even after tocilizumab appeared to be an indicator of failure of treatment.
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Keywords: Cytokine Storm; Immunosuppressive Drug; Interleukin-6 Inhibitor

Introduction

In December 2019, a newly discovered coronavirus, severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) caused the novel coronavirus disease of 2019 (COVID-19), that spread rapidly to become a pandemic. Around 80% of patients had a mild course, around 20% needed hospitalization (14% had severe disease and 5% were critical) and the overall case fatality rate was 2– 3% (1). Common symptoms at the onset of the disease included fever, cough, myalgia, fatigue, dyspnea, and diarrhea (2). Most of the patients who required hospitalization had pneumonia, which rapidly worsened into respiratory failure, and developed Acute Respiratory Distress Syndrome (ARDS) (2-3). Higher susceptibility and mortality were observed in elderly and patients with comorbidities (4).

It was proposed that, COVID-19 may be associated with a dysregulated immune response and hyperinflammation, which can lead to or exacerbate acute respiratory distress syndrome and multiorgan failure (5-7). Studies reported that higher levels of interleukin-6 positively correlated with cases of critical and severe COVID-19, whereas lower levels of interleukin-6 correlated with mild disease (8,9). In addition, it was reported that elevated levels of interleukin-6 are predictive of the likelihood of the need for mechanical ventilation (10).

Tocilizumab, an anti– interleukin-6 (IL-6) receptor monoclonal antibody, has been approved for the treatment of multiple inflammatory diseases (11,12) and appeared to improve outcomes in patients with COVID-19 pneumonia

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in observational studies in the United States and globally (13,14). According to local guidelines at our hospital, tocilizumab was recommended for COVID-19 patients with confirmed presence of severe disease, preferably within 24 to 48 hours of onset of severe disease/ICU admission, pneumonia, lung infiltrates, oxygen saturation ≤93%, and elevated inflammation markers (ferritin, CRP, IL-6) (15). Randomized trials investigating tocilizumab's efficacy have yielded diverse outcomes across different levels of COVID-19 severity and standards of care. Tariq et al. suggested potential benefits such as shorter vasopressor support duration, though with non-significant improvements in clinical outcomes (16). Gupta et al., observed a possible reduction in in-hospital mortality among critically ill patients treated early with tocilizumab, acknowledging potential confounding factors (17). Conversely, Salvarani et al., and Rosas et al., found no significant benefits in disease progression, clinical status, or mortality with tocilizumab (18,19). Therefore, further research, is warranted to clarify role of tocilizumab in COVID-19 treatment.

Hence, a retrospective analysis of outcomes following the use of tocilizumab is essential in order to understand the utility of tocilizumab in COVID 19 patients and better preparation for future phases of the pandemic. Therefore, this study was conducted to assess the association of various physiological factors, co-morbidities, severity of disease, laboratory parameters, and co-administered drugs with the outcome following tocilizumab administration in COVID-19 patients.

Methods

This is a retrospective observational study conducted at BJ Govt Medical College and Sassoon General Hospital, Pune. All COVID-19-positive patients admitted to Sassoon General Hospital, Pune who received Inj. Tocilizumab by their treating physician between 1 June 2020 to 31 July 2020 were included in the study.

The study commenced after approval by the Institutional Ethics Committee of BJGMC & SGH, Pune. Case papers of the patients who satisfied the study criteria were obtained from the medical record section of the hospital. Information related to physiological factors-age, gender, comorbidities, symptoms/severity of disease at admission, laboratory parameter (alkaline phosphatase, amylase, bilirubin total, bilirubin direct, CK MB, calcium, potassium, sodium, ferritin, blood sugar level, IL-6, LDH, pro-BNP, procalcitonin, protein albumin, protein total, SGOT, SGPT, urea, uric acid, hemoglobin, hematocrit, neutrophil, lymphocytes, RBC, WBC, d-dimer, platelets), drugs administered and outcome was noted in the study specific case record form. National Early Warning Score NEWS(20) which is based on the vital signs (respiratory rate, oxygen saturation, temperature, blood pressure, pulse/heart rate, AVPU response) and serves as a guide to quickly determine the degree of illness of a patient was also calculated for all participants of the study.

Data from case record form was analyzed to study the association of the physiological factors, comorbidities, severity of disease, laboratory parameters, and co-administered drugs with the outcome following tocilizumab administration in COVID-19 patients.

Comparison of characteristics of patients who survived versus those who died following therapy with tocilizumab was performed. 'Chi-square test' was used for the comparison of categorical data between survivors and non-survivors, while continuous data, like age and inflammatory markers were compared between survivors and non-survivors using 'Unpaired T test'. Comparison of values before and after tocilizumab administration was done using the 'Paired T test'. A p-value of less than 0.05 was considered as significant.

Mantel-Haenszel analysis was performed to assess whether NEWS score, hypertension, and hydroxychloroquine usage were directly associated with the outcome or if there was any kind of confounding or effect modification.

Results

A total of 25 patients received tocilizumab between 1 June 2020 to 31 July 2020, at our hospital. The tocilizumab dose administered was 4mg/kg body weight. A repeat dose of tocilizumab was administered to 10 of these 25 patients as per the decision of the clinician. The outcome was categorized as death or discharge and of these 25 patients, 7 patients survived while 18 patients died.

Patients were between the age group of 39-78 years; and the mean age of the patients was 54.12+ 11.86 years. The average hospital stay was 13.48 days. Mean duration of symptoms before admission was 4.48+ 1.04 days. Oxygen saturation at admission was in the range of 82-95%. During hospitalization, 28% of patients required non-invasive ventilation while 72% of patients were on invasive ventilation.

When the data was analyzed for the physiological factors-age and gender, it was observed that 10 out of 18 non-survivors were males (55.55%) while out of the 7 patients who survived, 6 were males (85.7%) (p= 0.16). The mean

age of patients among survivors was 43.57+7.84 and among non-survivors it was 58.22+10.65. In the study population, 12 patients out 25 of were middle-aged adults (36-55 years), among whom mortality was seen in 6 patients, while in the 13 patients above 55 years, only 1 survived (mortality was 92.31%) (p= 0.001).

The symptoms recorded in patients were sore throat (12%; p=0.11), fever (52%; p= 0.73), chest pain (4%; p= 0.53), headache (16%; p= 0.29), GI symptoms (16%; p= 0.88), cough (12%; p= 0.94), fatigue (2%; p= 0.66), altered sensorium (12%; p= 0.53), anosmia (12%; p= 0.11), loss of taste (12%; p= 0.11), shortness of breath (76%; p= 0.17). The survivors and non-survivors did not differ with respect to symptoms of illness. (Table 1)

In our study population, 15 patients had high NEWS score (death occurred in all), 6 patients had medium NEWS score (death: 33.33%; discharge: 66.66%) and 4 patients had low NEWS score (death: 25%; discharge: 75%) (OR:12.43; p= 0.0004).

Analysis of comorbidities revealed that 10 patients were suffering from diabetes mellitus (death:32%, discharge:8%; p= 0.43), 7 from hypertension (death: 32%, discharge: 8%; p= 0.05), 1 from asthma (death: 4%, discharge: 0%; p= 0.53), 1 from obesity (death: 4%, discharge: 0%; p= 0.53), and 3 from ischemic heart disease (death: 4%, discharge: 8%; p= 0.11).

It was noticed that, 15 of patients received single dose of tocilizumab of which 12 (80%) expired and 10 received a second dose of Toclizumab of which 6 (60%) expired (p= 0.28). Other anti-inflammatory agents prescribed to study population were Inj. Methyl prednisolone (MPS) (death:13; discharge:7; p= 0.21), Inj. Dexamethasone (death: 7; discharge: 1; p= 0.21) and T. Prednisolone (death:8; discharge:1; p= 0.81). Patients in the study population received antibacterial drugs like Piperacillin+ Tazobactam (death:16; discharge:7 ;p= 0.61), Metronidazole (death: 48%; discharge: 16%; p= 0.82), Augmentin (death:3; discharge:1; p= 0.88), Meropenem (death:12; discharge: 4; p= 0.66), Vancomycin (death:1; discharge: 0; p= 0.53) in injectable form, and orally T. Augmentin (death:1; discharge:2; p= 0.11) and T. Doxycycline (death:8; discharge:3; p= 0.94). Anticoagulant prescribed to the patients were Inj. Clexane (death:15, discharge:6; p= 0.26) and Inj. Heparin (death; discharge:1; p= 0.97). Cardioactive drugs administered were Inj. Digoxin (death: 0; discharge: 1; p= 0.1), Inj. Furosemide (death: 12; discharge: 2; p= 0.17), T Enalapril (death: 1; discharge: 2; p= 0.21), T. Atenolol (death:4; discharge:1; p= 0.66). Subcutaneously Insulin (death: 8, discharge:2; p= 0.41) and orally T. Metformin (death:1, discharge:0; p= 0.47), T. Glimipride (death:1; discharge:0; p= 0.47) were the anti-diabetic drugs prescribed. Miscellaneous drugs like T. Ivermectin (death:9; discharge:2; p= 0.34), T. HCQ (death:15; discharge:2; p= 0.009), Cap. Favipiravir (death:5; discharge:4; p= 0.96) were prescribed.

Overall analysis revealed that NEWS score, hypertension and hydroxychloroquine usage was significantly associated with worst outcome (p<0.005). Mantel-Haenszel analysis assessed the direct association of factors with the outcome and identified hypertension as insignificant, while hydroxychloroquine usage showed a trend for association with worst outcome.

Both pre-tocilizumab and post- tocilizumab levels of laboratory parameters were analyzed for association with outcome but none were statistically significant. Alkaline phosphatase, amylase, bilirubin total, bilirubin direct, CK MB, calcium, potassium, sodium, ferritin, blood sugar level, IL-6, LDH, pro-BNP, procalcitonin, protein albumin, protein total, SGOT, SGPT, urea, uric acid, hemoglobin, hematocrit, neutrophil, lymphocytes, RBC, WBC, d-dimer, platelets were studied. Qualitative analysis showed that a similar percentage of patients in both outcome group had derangement of lab parameters including inflammatory markers. (Table 2)

While analyzing inflammatory markers, it was observed that non-survivors exhibited elevated pre- and post-tocilizumab values of IL-6 levels (p= 0.0011) and higher post-treatment ferritin levels (p: 0.019), along with a rise in ferritin levels following tocilizumab administration (p= 0.029). (Table 3)

Table 1. Presenting symptoms at time of hospitalization.

Symptoms	Death	Discharge	P value
Sore throat	1	2	0.11
fever	9	4	0.75
Chest pain	1	0	0.53
Headache	2	2	0.29
GI symptoms	3	1	0.88
Cough	8	4	0.94
Fatigue	6	3	0.66
Altered Sensorium	1	0	0.53
Anosmia	0	0	Na
Siezures	0	0	Na
Loss of taste	1	2	0.11
Shortening of breath	15	4	0.17

Table 2. Number of patients showing derangement of Lab Parameters Pre & Post Tocilizumab among survivors and non-survivors

Lab Parameters	Death	Discharged	P value
Alkaline phosphatase			
Pre dose	1	2	0.36
Post dose	1	0	0.53
Amylase			
Pre dose	3	0	0.25
Post dose	2	0	0.36
Billirubin total			
Pre dose	5	2	0.96
Post dose	2	2	0.29
Billirubin direct			
Pre dose	6	0	0.08
Post dose	2	0	0.36
CK MB			
Pre dose	16	7	0.36
Post dose	12	7	0.15
Calicum			
Pre dose	6	3	0.66
Post dose	3	2	0.51
Creatinine			
Pre dose	3	2	0.51
Post dose	3	1	0.88
Potassium			
Pre dose	0	0	NaN
Post dose	1	0	0.53
Sodium			
Pre dose	0	0	NaN
Post dose	0	0	NaN
Ferritin			
Pre dose	17	6	0.47
Post dose	17	6	0.47
IL-6			
Pre dose	18	7	NaN
Post dose	18	7	NaN
LDH			
Pre dose	3	2	0.51
Post dose	3	1	0.88
Procalcitonin			
Pre dose	5	2	0.96
Post dose	4	2	0.74

Lab Parameters	Death	Discharged	P value
Protein albumin			
Pre dose	5	0	0.12
Post dose	3	0	0.25
Protien total			
Pre dose	2	0	0.36
Post dose	2	0	0.36
SGOT			
Pre dose	7	1	1.000
Post dose	7	1	1.000
SGPT			
Pre dose	5	2	0.96
Post dose	4	2	0.74
Urea			
Pre dose	15	4	0.17
Post dose	14	5	0.74
Uric acid			
Pre dose	1	1	0.47
Post dose	1	1	0.47
Hemoglobin			
Pre dose	2	1	0.82
Post dose	2	1	0.82
Hematocrit			
Pre dose	2	0	0.36
Post dose	2	0	0.36
Neutrophil			
Pre dose	18	7	NaN
Post dose	18	7	NaN
Lymphocytes			
Pre dose	18	6	0.10
Post dose	18	6	0.10
Platelets			
Pre dose	5	2	0.96
Post dose	4	2	0.74
D.dimer			
Pre dose	15	2	0.09
Post dose	15	2	0.09
WBC			
Pre dose	18	7	NaN
Post dose	18	7	NaN
RBC			
Pre dose	3	2	0.29
Post dose	2	2	0.5

Table 3. Levels of Inflammatory Markers relevant to COVD -19 among survivors and non-survivors.

Marker	Time with reference to Tocilizumab dose	Death	Discharge	P value death v/s discharge	P value pre v/s post
IL-6	Pre	570.11±498.76	110.31± 49.68	0.0011	Death: 0.109981
	Post	1042.889±1143.126	112.5714±41.18599	0.003053	Discharge:0.797507
Ferritin	Pre	1168.722±838.1637	807.5714±479.4194	0.193617	Death:0.029299
	Post	1756.5± 1622.03	711.71± 421.23	0.019	Discharge:0.395567
D.dimer	Pre	3.328333±4.656725	2.531429±4.409249	0.696912	Death:0.099949
	Post	5.882222±6.772023	3.291429±4.385633	0.275785	Discharge:0.621419

Discussion

This was a retrospective observational study to assess the association between physiological, pharmacological, biochemical, clinical factors with outcomes following of tocilizumab administration. Physiological factors assessed were gender and age, which showed that patient with higher age group had less chances of survival, in spite of giving tocilizumab treatment. There is correlation between age and natural immunity as reviewed elsewhere and it has been concluded that older people are particularly prone to develop more infections as natural immunity declines gradually at older ages (21). Older people are also vulnerable to adverse drug reactions which may be partly because of the either reduced organ function at older age or taking multiple drugs due to comorbidities (22). The impact of these factors on reduced survival among the elderly cannot be disregarded. NEWS score is a tool developed by the Royal College of Physician which improves the detection and response to clinical deterioration in adult patients and is a key element of patient safety and improving patient outcomes (23). In our study we observed that patients with high NEWS score are less likely to survive covid infection, despite administration of tocilizumab therapy.

Primary analysis revealed that high NEWS score, hypertension and hydroxychloroquine administration was associated with poor outcome, but after Mantel-Haenszel adjustment it was found that hypertension was not associated with outcome while hydroxychloroquine usage showed a trend. It appeared that patients with high NEWS score were prescribed a greater number of drugs and hydroxychloroquine was a part of the treatment. Thus, it was probably just a coincidental finding that hydroxychloroquine usage was associated with poor outcome. Thus, NEWS score was the primary factor associated with mortality. In a French cohort study, which aimed to determine whether the NEWS score at admission can accurately predict in-hospital mortality, the result showed that, high NEWS score at admission is independently associated with worst outcome. In daily practice, a NEWS score > 6 at the time of admission may help to identify high risk patients (24).

Although there is no established cut off value for interleukin 6 level to predict a higher likelihood of cytokine release syndrome. Measurement of inflammatory biomarkers may guide clinicians to select appropriate patients for immunosuppressive therapy (25). High interleukin 6 and other inflammatory biomarkers was used to support the role of cytokine storm in clinical presentation of our patients. In our study we found out, high pre dose interleukin 6 levels were associated with poor outcome in the study population. One of the conclusions could be that, in such patients, the dose of tocilizumab that was used may have been inadequate to countering IL-6 levels. Thus, higher levels of IL-6 may require higher dose of tocilizumab and may be a determinant of tocilizumab dose. Hence, further study should be designed in order to test the above hypothesis.

Tocilizumab has been approved by the FDA for certain inflammatory disorders and highly recommended by the expert panel for the treatment of COVID-19- cytokine storm in hospitalized patients (26). Different metanalyses and systematic reviews were published on the efficacy of tocilizumab treatment in COVID-19 patients with contradictory findings. (27,28,29) The latest and largest was the Rapid Evidence Appraisal for COVID-19

Therapies (REACT) meta-analysis that included 27 RCTs with a total of 10930 COVID-19 patients and 6,449 patients treated with IL-6r antagonists (IL-6Ra), representing 90% of all COVID-19 patients registered in IL-6Ra research trials (28). The meta-analysis reported a significant reduction in all-cause 28-days mortality compared to placebo or standard care for tocilizumab (OR: 0.83 [95% CI: 0.74-0.92]). Moreover, most of the reported RCTs were able to distinguish groups of patients receiving corticosteroids at randomization (22 trials). Interestingly, there was a significant interaction between IL-6 antagonists and corticosteroids. Indeed, concomitant administration of corticosteroids and tocilizumab resulted in further decreases in the 28-days all-cause mortality compared to placebo or standard of care (OR: 0.77 [95% CI: 0.680.87]). Also, concomitant use of tocilizumab and corticosteroids resulted in less likelihood of progression to invasive mechanical ventilation, ECMO, or death at 28-days compared to placebo or standard of care (OR: 0.69 [95% CI: 0.61-0.78]).

The optimal timing of tocilizumab use was not addressed in the prospective REACT meta-analysis (28). However, the REMAP-CAP trial demonstrated a hazard ratio of 1.59 (95% C: 1.24-2.05) for increased 90-days probability survival in patients who received tocilizumab in the first 24 h after ICU admission (30).

The Guideline Development Group (GDG) have made a strong recommendation for use of IL-6 receptor blockers (tocilizumab and sarilumab) or baricitinib as alternative agents administered in addition to corticosteroids for patients with severe or critical COVID-19, but had elected to refrain from recommending combining these three immunosuppressive drugs until clear evidence of incremental benefit emerged. The RECOVERY trial has now provided this evidence that combining corticosteroids, IL-6 receptor blockers and baricitinib provides incremental survival benefits (31). Specifically, in RECOVERY 2659 patients received baricitinib along with corticosteroids and IL-6 receptor blockers.(32) The effect of baricitinib in this subgroup was consistent with the beneficial effect of baricitinib in patients who were not treated with IL-6 receptor blockers (31). Although these three immunosuppressive drugs are recommended and may be administered jointly, the panel anticipated that there would be situations where clinicians may opt for less aggressive immunosuppressive therapy and/or to combine medications in a stepwise fashion in patients who are deteriorating. However, since the drugs have not undergone direct comparisons, if this situation arises, the GDG felt that clinicians should choose between baricitinib and IL-6 receptor blockers on the basis of experience and comfort using the drugs; local institutional policies; route of administration (baricitinib is oral; IL-6 receptor blockers are intravenous); and cost.

The GDG also noted that, compared with some other candidate treatments for COVID-19, IL-6 receptor blockers are more expensive and the recommendation does not take account of cost-effectiveness. Currently, access to these drugs is challenging in many parts of the world, and without concerted effort is likely to remain so, especially in resource-poor areas. It is therefore possible that this strong recommendation for IL-6 receptor blockers could exacerbate health inequity. On the other hand, given the demonstrated benefits for patients, it should also provide a stimulus to engage all possible mechanisms to improve global access to these treatments. Individual countries may formulate their guidelines considering available resources and prioritize treatment options accordingly. At a time of drug shortage, it may be necessary to prioritize use of IL-6 receptor blockade through clinical triage (31) Many jurisdictions have suggested mechanisms for triaging use of these treatments. These include prioritizing patients with the highest baseline risk for mortality (e.g. those with critical disease over those with severe disease), in whom the absolute benefit of treatment is therefore greatest. For example, despite consistent relative effects (OR 0.86 f or mortality) with IL-6 receptor blockers, the absolute risk reduction for mortality in the critically ill would be 31 fewer deaths per 1000 (95% CI 11 to 47 fewer deaths) and in the severely ill would be 13 fewer deaths per 1000 (95% CI 5 to 19 fewer deaths). Other suggestions for prioritization, include focusing on patients with an actively deteriorating clinical course and avoiding IL-6 receptor blocker therapy in those with established multi-organ failure (in whom the bene fit is likely to be smaller). As IL-6 receptor blockers require intravenous administration, this treatment would be primarily indicated for patients with severe and critical COVID-19 who require hospitalization. IL-6 receptor blockers are relatively easy to administer, and only require one, or at most, two doses.

In the present study, we have tried to identify physiological, clinico-pathological, biochemical, and pharmacological parameters that may help in triaging IL-6 receptor blockers. We observed that currently used dose of tocilizumab failed to provide survival benefit among the patients above 55 years of age, those receiving hydroxychloroquine, patients with high NEWS score at admission, patients with high IL-6 values and those

showing rising ferritin levels.

Our study has outcome limitations that require careful interpretation of the findings and may affect the generalizability of the results. First, the study design was retrospective in nature where the outcome has already occurred. Such retrospective study design is inherently inferior to randomized controlled trials but never the less helps to generate a hypothesis. Second, this single-center cohort study with small sample size, hence it was not feasible to perform propensity score matched analysis. Third, timing of administration of tocilizumab could be crucial factor in determining its effectiveness. Some researchers claim that the optimal time to prescribing tocilizumab is in beginning of inflammation and first steps of dropping O2 saturation (25). But as the study was retrospective observational, it was beyond control of the investigator to decide the timing of tocilizumab administration.

In Covid 19 patients with cytokine storm, older age group, high NEWS score, high pre-dose IL-6 levels and rise in post treatment ferritin level was associated will a poor response to tocilizumab. Thus, despite being an anti-interleukin 6 antibody, tocilizumab could not abort cytokine storm with above mention characteristics. Thus, given the retrospective nature and small sample size of the study, it appears that randomized controlled trials and higher doses of tocilizumab (based on IL-6 level) may provide better information regarding its utility.

Conflict of interest

The author declares no conflict of interest, financial or otherwise.

References

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239–42.
2. Chen N, Zhou M, Dong X, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet.2020; 395 (10223):507–513.
3. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-1069.
4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
5. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395:507-13.
6. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395:1033-4.
7. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe. 2020;27(6):992-1000.e3.
8. Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: a metaanalysis. J Med Virol. 2020;92:2283-5.
9. Zhu J, Pang J, Ji P, et al. Elevated interleukin-6 is associated with severity of COVID-19: a meta-analysis. 2021;93(1):35-37
10. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID19. J Allergy Clin Immunol. 2020;146(1): 128-136.e4.
11. Actemra prescribing information. South San Francisco, CA: Genentech, 2019 (package insert).
12. RoActemra summary of product characteristics. Grenzach-Wyhlen, Germany: Roche, 2020.
13. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci USA. 2020;117:10970-5.
14. Morrison AR, Johnson JM, Griebe KM, et al. Clinical characteristics and predictors of survival in adults with coronavirus disease 2019 receiving tocilizumab. J Autoimmun. 2020;114:102512.
15. Ministry of Health and Family Welfare. Clinical management protocol for COVID-19. [Internet]. 2020 [cited 2020 June 27]. Available from: https://www.mohfw.gov.in/pdfnagementProtocolforCOVID19dated27062020.pdf
16. Tariq K, Covut F, Al-Jaghbeer MJ, Rose L, Gopalakrishnan KV, Akbik B. Tocilizumab for

treatment of patients with severe COVID-19: A retrospective cohort study. EClinical Medicine. 2020;24:100418.

17. Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. JAMA Intern Med. 2020 October 20 (Epub ahead of print).

18. Salvarani C, Dolci G, Massari M, 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.

19. Rosas I, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with COVID-19 pneumonia. September 12, 2020 (https://www.medrxiv.org/content/10.1101/ 2020.08.27.20183442v2). preprint.

20. News score calculated : https://www.mdcalc.com/national-early-warning-score-news

21. Leng J, Goldstein DR. Impact of aging on viral infections. Microbes Infect. 2010;12(14–15):1120–4.

22. Lavan AH, Gallagher P. Predicting risk of adverse drug reactions in older adults. Ther Adv Drug Saf. 2016;7(1):11–22.

23) https://www.england.nhs.uk/ourwork/clinical-policy/sepsis/nationalearlywarningscore

24. Pokeerbux MR, Yelnik CM, Faure E, et al. Lille Covid-team.National early warning score topredict intensive care unit transfer and mortality in COVID-19in a French cohort. Int J Clin Pract. 2021;00:e14121.

25. Mehta P, McAuley DF, Brown M, et al. COVID_19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395 (10229):1033._4.

26. Samaee H, Mohsenzadegan M, Ala S, Maroufi SS, Moradimajd P. Tocilizumab for treatment patients with COVID-19: Recommended medication for novel disease. Int Immunopharmacol. 2020;89(Pt A):107018.

26. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/table--characteristics-of-immunomodulators/

27. Ghosn L, Assi R, Evrenoglou T, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. Cochrane Database Syst Rev. 2023;6(6):CD013881.

28. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. JAMA. 2021;326(6):499-518.

29. Snow TAC, Saleem N, Ambler G, Nastouli E, Singer M, Arulkumaran N. Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials. Intensive Care Med. 2021;47(6):641-652.

30. Brown MJ, Alazawi W, Kanoni S. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021;385(12):1147.

31. Therapeutics and COVID-19: Living guideline, 13 January 2023, https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2023.1

32. RECOVERY Collaborative Group. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomized, controlled, open-label, platform trial and updated meta-analysis. Lancet. 2022;400(10349):359-368.

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