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ORIGINAL RESEARCH

Secondary Infections in Patients with COVID-19 Pneumonia Treated with Tocilizumab Compared to Those Not Treated with Tocilizumab: A Retrospective Study at a Tertiary Hospital in Kenya

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Introduction: From the first case of SARS-Co-2 in Wuhan, China, to the virus being declared as a pandemic in March 2020, the world has witnessed morbidity and mortality on a global scale. Scientists have worked at a record pace to deliver a vaccine for the prevention of this deadly disease. Tocilizumab, an interleukin-6 (IL-6) blocker, received an emergency use authorization (EUA) by the Federal Drug Agency (FDA) in June 2021.

Methods: This retrospective observational cohort study was conducted at the Aga Khan University Hospital, Nairobi, from March 8, 2020, to December 31, 2020. All patients with PCR confirmed COVID-19 pneumonia were included. Data were obtained from the medical records, and the admission registry was used to identify the patients, and both their electronic and paper-based files were retrieved from the medical records. Patient demographic data, medical history, baseline comorbidities, clinical characteristics, and outcome data were collected to study the infectious complications of Tocilizumab in patients affected by COVID-19 pneumonia.

Results: A total of 913 patients who were diagnosed with COVID-19 were included. The overall superinfection infection rate among the COVID-19 patients was 6%. Superinfection in patients who received the Tocilizumab was 17.2% and in the non-Tocilizumab group was 4.8%. The superinfection rate among severe and critically ill patients was even higher at 41.8% and 69.9% (Tocilizumab group) and 2.1% and 11.8% (non-Tocilizumab group), respectively ($p < 0.001$). There was no difference in mortality observed between the groups ($p = 0.846$). Infection among HIV co-infection was very low at 2.3%.

Conclusion: Contrary to some studies, a higher rate of infection was observed among the Tocilizumab group, and no difference in mortality was observed between Tocilizumab and the non-Tocilizumab group. Infection among patients with HIV remains low in this susceptible population.

Keywords: COVID-19, SARS-CoV-2, EMPACTA, RECOVERY, Tocilizumab, IL-6, REMDATA, CONVACTA

Introduction

In December 2019, the first case of SARS-CoV2 was discovered in Wuhan, China, linked to an outbreak in the seafood market.[1] It was later named COVID-19. Within months, the virus rapidly spread to several countries, and by March 11, 2020, it was labeled a pandemic by the World Health Organization (WHO).[2] As of December 18, 2021, approximately 281 million people globally have been infected, with approximately 5.4 million deaths resulting from the virus.[3] These numbers may be the tip of the iceberg, as most developing countries have poor data collection and public health reporting systems, especially within rural communities.

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Numerous trials have yielded controversial results, and multiple trials are still in process. So far, treatment options remain limited, with steroids in the forefront, followed by Tocilizumab or Baricitinib in COVID-19 patients with cytokine storm.

Tocilizumab is a monoclonal antibody with activity against the interleukin-6 (IL-6) receptors. It has been approved for the treatment of Rheumatoid arthritis, Systemic Juvenile Idiopathic Arthritis, life-threatening cytokine release syndrome, Giant Cell Arteritis, most recently received emergency use authorization for COVID-19.[4–9] IL-6 is produced by various cells in response to inflammation, infection, trauma, or immunological attack. Tocilizumab is a monoclonal antibody that competitively inhibits the binding of IL-6 to both membrane and soluble IL-6 receptors.[10,11]

Elevated levels in IL-6 have been observed in patients with COVID-19.[12] Several small studies, both cohort and retrospective studies, have demonstrated the beneficial effects of using Tocilizumab.[13–15] The decision of the Federal Drug Administration (FDA) for emergency use approval of Tocilizumab in combination with steroids in patients who require oxygen or invasive and non-invasive life support came from the data supported by the RECOVERY trial, CONVACTA Trial, EMPACTA trial, and the REMDACTA trial.[11,15–17]

Treatment with an IL-6 blocker is associated with a higher risk of infections.[18] It is important to note that late-onset infection has been more commonly seen in patients who have used Tocilizumab when compared to the control group.[19–22]

Kenya is Tuberculosis (TB) endemic country with higher burdens of TB in urban settings (760 per 100,000) compared to rural settings (453 per 100,000 population). There is also a higher TB incidence among the elderly (65+ years). Kenya is also HIV endemic, with a prevalence rate of 4.9%. Due to Kenya's status as a high burden country for both TB and HIV, there have been concerns that further immunosuppressing these patients with Tocilizumab may increase the number of TB and make way for opportunistic infections in these patients.[23]

Both WHO and NIH have endorsed Tocilizumab to treat cytokine storm crisis among patients with COVID-19. However, the data regarding the infectious complications related to the use of Tocilizumab is limited, especially in developing countries where there is a high prevalence of infectious and HIV diseases. We undertook the retrospective chart review study to look at the rate of superinfection among patients treated with the Tocilizumab and a non-Tocilizumab group of the patients at a tertiary hospital in Kenya to address this issue.

Methods

A retrospective observational cohort study was conducted involving patients admitted for COVID-19 and bacterial or fungal coinfection/superinfection between March 8 and December 31, 2020. The study was conducted at the Aga Khan University Hospital, Nairobi (AKUHN), a 258-bed, private, not-for-profit, tertiary-level teaching and referral hospital.

All COVID-19 patients (children and adults: age 0 and above) with the confirmed diagnosis were enrolled based on positive real-time reverse transcription-polymerase chain reaction (RT-PCR) assays for SARS-CoV-2 from a nasopharyngeal swab. Lower respiratory samples were obtained if the nasopharyngeal swab was negative and if there was a high clinical index of suspicion. Patients discharged from the emergency department were excluded. All co-morbidities were included. Including TB and HIV as we are a TB endemic country with a high national HIV prevalence. In the initial months of the pandemic, it was mandated by the Ministry of Health, Kenya, to isolate all patients in health facilities for management and care due to the rising number of COVID-19 cases. This was later changed to admit only those who required supplemental oxygen and presented with comorbidities. Therefore, the severity of disease in hospitalized patients evolved with the pandemic, with patients ranging from asymptomatic to severe in the initial months, to only severe/critical and those with co-morbidities in the later months.

Ethical approval for this study was obtained from the Institutional Ethics Review Committee at AKUHN. A waiver for informed consent was obtained as it was a retrospective study. All related procedures were followed in accordance with the Declaration of Helsinki. No patient identifiers were used, and data were abstracted from the medical chart records into the REDCap platform.

Laboratory Procedures

SARS-CoV-2 infection was confirmed by real-time reverse transcriptase PCR (RT-¬PCR) assay (QuantStudio5- Applied Biosystems Thermo Fisher Scientific and MiC PCR from Bimolecular Systems) from nasopharyngeal swabs (Thermo Fisher Scientific) and viral transport media (CAPRICORN Scientific).

The microbiology laboratory at AKUHN is an accredited laboratory by the College of American Pathologists (CAP). The lab has consistently maintained external QC and proficiency testing scoring between 90–100%.

Blood cultures were performed using a fully automated BD Bactec FX 40 system using BD Bactec plus aerobic and anaerobic media, which fully support the yeast growth from blood. All culture and susceptibility tests were performed using standard microbiology procedures.[24–26]

All clinically significant bacterial and yeast isolates were identified using Vitek 2 60 (bioMerieux Inc). The Vitek 2 60 system uses a fluorogenic methodology for organism identification and a turbidimetric method for susceptibility testing. Supplemental Disk diffusion and E tests were also used wherever applicable depending on the drug and pathogen combination (VITEK YST ID Card - Reference number 21343, VITEK2 Antifungal AST card -YS 08 Ref. 420739).

Vitek AST cards use CLSI breakpoints for the interpretation of antimicrobial and antifungal susceptibilities.[25,26]

Definitions

Diagnosis of a significant infection was based on the clinical presentation, the isolation of an etiological agent, and the assessment of the group of clinicians responsible for the patient. Bacteremia/fungemia was defined as the isolation of a pathogen in one or more blood cultures. For microorganisms of the cutaneous flora, its growth was assessed in two or more blood cultures extracted by different routes.

Coagulase-negative staphylococci were usually considered contaminants in blood culture unless repeatedly isolated from multiple blood cultures, or patients had the clinical background to consider them pathogens, eg, endocarditis, presence of prostheses, etc.

For catheter-associated bacteremia (CAB), isolation of the same pathogen from blood and the catheter tip (> 15 colonies on sheep blood agar plate) was considered significant, as well as pathogens from blood samples obtained in parallel or in two blood cultures extracted simultaneously from the catheter and by venipuncture. Respiratory infection (RI) was considered if there was significant isolation of a potentially pathogenic microorganism in bronchoalveolar lavage (BAL), in a bronchial aspirate (BAS), or in a sputum sample with an acceptable Q score (> +1).

Urinary tract infection (UTI) was defined as isolation of a uropathogen, significant colony count with or without pyuria in a patient's urine sample with signs and/or symptoms of UTI. The diagnosis of skin and soft tissue infection (IPPB) was based on the direct Gram stain (PMN and presence of bacteria or fungi) culture isolation of a significant pathogen from a standard clinical sample.

Intervention

Tocilizumab was included in our internal institutional protocol for the treatment of COVID-19, specifically for use in patients with progressive clinical deterioration, increasing oxygen requirements, and elevated inflammatory markers at the discretion of the treating team and infectious diseases consultation service. Our protocol recommended a dose of 8mg/kg Tocilizumab administered intravenously with the potential for redosing based on clinical response (eg, oxygenation status, hemodynamic stability, inflammatory marker response). Tocilizumab was not used in patients with deranged liver function test (LFT) with AST and ALT five-time upper limit of normal detected within 24 hours of screening. Patients with significant cytopenia or documented ongoing infection were also excluded. Similarly, patients enrolled in any other clinical trials were not eligible to receive Tocilizumab.

Data Collection

Data were collected by a research assistant from the medical records department using manual and electronic health records for all patients admitted with a diagnosis of critical COVID-19 prior to the study period. The data were extracted and entered into a REDCap© database.[27] Variables were grouped into demographic data, comorbidities such as diabetes,

hypertension, heart disease, HIV status, COPD, renal disease, cancer and rheumatology disorders, risk factors such as COVID-19 severity, number, and type of infection, microbiological data, diagnostic imaging tests, antibiotic treatment (empirical and directed), and evolution during hospital admission. The patients were grouped into two categories according to their admission to the ICU. Patients with microbiological isolates considered contaminants were excluded from the study. After data collection and coding, the data collected was exported to SPSS for analysis (IBM Statistical Package for the Social Sciences version 20.00).

Statistical Analysis

Categorical data were summarized as frequencies and percentages, whereas continuous data were summarized as means and standard deviations (SD). The normality of the data was analyzed using the Shapiro Wilk test for continuous data. Differences between groups with those given Tocilizumab versus non-Tocilizumab group were analyzed using Student's *t*-test or the Wilcoxon-Mann–Whitney test (depending on the normality of the data) for continuous variables and using Chi-square (χ^2) or Fisher's exact test for categorical variables. A p-value of < 0.05 was considered significant.

Results

Nine hundred thirteen patients were diagnosed with COVID-19 between March 8th 2020-December 31st, 2020. The mean age of the patients diagnosed with COVID-19 was 51.17 (SD=16.66), and 66.5% of the patients were male. Details of demographics and comorbidities are shown in Table 1. The patient in the Tocilizumab group was older than the non-Tocilizumab group. There was no difference in the morbidity among the group except hypertension which was more prevalent among the Tocilizumab group (Table 1). 93 of the 913 patients received Tocilizumab (10.2% - Tocilizumab group) and 820 of the 913 did not receive Tocilizumab (89.8% - non-Tocilizumab group). In the non-Tocilizumab group, 38 patients (4.6%) were on mechanical ventilation, In the Tocilizumab group, 40.9% (38/93) were on mechanical ventilation, whereas 59.1% (55/93) were not on mechanical ventilation. The overall infection rate among the COVID-19 patients was 6%. Only 4.8% (39/820) of patients had an infection in the non-Tocilizumab group, whereas 17.2% (16/93) had an infection in the Tocilizumab group ($p<0.001$). Infection in patients who had the severe and critical illness in the non-Tocilizumab group was 43% and 3.5%, respectively, whereas in the Tocilizumab was 47.3% and 37.6%, respectively, which was statistically significant ($p<0.001$). There was no difference in the mortality between patients between the two groups (Table 2). Moreover, no difference in mortality between the groups was observed, even when patients with severe and critical COVID-19 were considered (Table 3 and Figure 1). Of the patients who died, 36.4% (16/44) received mechanical ventilation and did not receive Tocilizumab, whereas 65.7% (23/35) received both mechanical ventilation and Tocilizumab.

Of the 55 patients that had infections, 47.3% of patients had one infection, and the remaining had more than one infection. Thirteen patients (23.6%) had more than four infections. The commonest site of infections was blood (26.4%) and tracheal aspirate (26.4%), followed by urine (20.7%) (Table 4). One hundred forty total infections were reported among the patients; the organisms and percentage among patients who did and did not receive Tocilizumab are shown in Table 5.

Discussion

Besides the therapeutics, the development of vaccines and emergence of the variant has also posed significant challenges. Results from the trials that evaluated the use of Tocilizumab in treating COVID-19 infection have been inconsistent.[28–30] Most studies have addressed hospital stay, mechanical ventilation, intensive care unit stay, or 28 days mortality.[11,15–17,31–36] The increased infection has not been the focus of these studies.

RECOVERY trial presented their findings from the large heterogeneous group. The RECOVERY trial primary outcome from all-cause mortality was 35% in the usual care group, and 31% in the Tocilizumab group (p=0.002) compared to our patients where mortality was 8.5 vs 9.7 (p=0.84). The infectious complications of Tocilizumab were not studied in the RECOVERY trial.

Table 1 Demographics of Patients with COVID-19

		Total (n = 913)		Tocilizumab				P value
				No (n=820)		Yes (n=93)		
Age (Years) (mean (39))		51.17	(16.66)	50.25	(16.51)	59.32	(15.80)	**<0.001**
Age (Years)	**0–17**	21	2.3%	20	2.4%	1	1.1%	**<0.001**
	18–39	218	23.9%	207	25.2%	11	11.8%	
	40–69	547	59.9%	494	60.2%	53	57.0%	
	> 70	127	13.9%	99	12.1%	28	30.1%	
Gender	**Male**	607	66.5%	535	65.2%	72	77.4%	**0.02**
	Female	306	33.5%	285	34.8%	21	22.6%	
Race	African	738	80.8%	671	81.8%	67	72.0%	**0.06**
	Indian	106	11.6%	89	10.9%	17	18.3%	
	Others	69	7.6%	60	7.3%	9	9.7%	
Baseline Comorbidities	**Diabetes**	249	27.3%	222	27.1%	27	29.0%	**0.713**
	Hypertension	300	32.9%	256	31.2%	44	47.3%	**0.002**
	Heart Disease	48	5.3%	43	5.2%	5	5.4%	**1**
	HIV Positive	21	2.3%	20	2.4%	1	1.1%	**0.714**
	COPD	4	0.4%	2	0.2%	2	2.2%	**0.054**
	Renal	37	4.1%	33	4.0%	4	4.3%	**0.784**
	Cancer	24	2.6%	19	2.3%	5	5.4%	**0.088**
	Rheumatology Disorders	6	0.7%	6	0.7%	0	0.0%	**1**
	Others	180	19.7%	159	19.4%	21	22.6%	**0.492**
	None	408	44.7%	375	45.7%	33	35.5%	**0.062**
Renal Disease	**Stage 2**	1	2.7%	1	3.0%	0	0.0%	**0.613**
	Stage 3	7	18.9%	7	21.2%	0	0.0%	
	Stage 4	29	78.4%	25	75.8%	4	100.0%	
Comorbidities	**None**	409	44.8%	376	45.9%	33	35.5%	**0.152**
	1	252	27.6%	223	27.2%	29	31.2%	
	≥ 2	252	27.6%	221	27.0%	31	33.3%	
Diabetes Overall		439	48.1%	390	47.6%	49	52.7%	**0.382**
Hypertension Overall		344	37.7%	303	37.0%	41	44.1%	**0.214**

The main concern for using Tocilizumab has been infection, especially among the patients with impaired T-cell immunity such as Tuberculosis, HIV/AIDS, or any immunocompromised status. These patients are usually excluded from these trials.

Table 2 Infection and Mortality Among Patient with and without Tocilizumab

	Total COVID-19 (n = 913)	Infection	Infection %	No-Tocilizumab Group (n=820)	No-Tocilizumab Group %	Tocilizumab Group (n = 93)	Tocilizumab Group %	
Bacterial/Fungal Infection	**No**	858	94.0%	781	95.2%	77	82.8%	**<0.001**
	Yes	55	6.0%	39	4.8%	16	17.2%	
Final Covid Severity	**Mild**	423	46.3%	409	49.9%	14	15.1%	**<0.001**
	Moderate	29	3.2%	29	3.5%	0	0.0%	
	Severe	397	43.5%	353	43.0%	44	47.3%	
	Critical	64	7.0%	29	3.5%	35	37.6%	
Outcome	**Recovered**	834	91.3%	750	91.5%	84	90.3%	**0.846**
	Died	79	8.7%	70	8.5%	9	9.7%	

Table 3 Mortality Among Patient with Severe and Critical COVID-19 with and without Tocilizumab

		Tocilizumab					
		No		Yes			
SEVERE COVID	Recovered	341	96.60%	40	90.90%	p value = 0.085	
	Died	12	3.40%	4	9.10%		
		Tocilizumab					
		No		Yes			
CRITICAL COVID	Recovered	5	17.20%	4	11.40%	p value = 0.720	
	Died	24	82.80%	31	88.60%		

Secondary infection in a patient receiving the Tocilizumab remains a critical concern in patients who are critically ill and especially receiving the IL-6 inhibitors, which have shown to have increased risk of infection, especially among the critically ill immunocompromised patients. In our study, the patients who received Tocilizumab had a higher risk of infection, which was statistically significant ($p<0.001$) when compared to patients who were in the non-Tocilizumab group. This may be because patients in then the Tocilizumab group were more critical and likely were more prone to the superinfection. On the contrary, in a meta-analysis looking at 24 studies with 1156 COVID-19 patients, investigators did not find any significant risk of infections or adverse effects in the Tocilizumab group.[20] Another trial conducted by WHO showed that secondary infection occurred in 21.9% of the patients in the IL-6 group vs 17.6% in the placebo or non-Tocilizumab group, which was not statistically significant (OR 0.99 CI: 0.85–1.16).[37]

Most infections in our patients were from blood, tracheal aspirates, and urine. The commonest infections were gram negatives, Escherichia Coli, Pseudomonas, Enterobacter Cloacae, and Klebsiella pneumonia. Gram-positive and fungal infections were less common. This reflects the pattern of infections seen in hospitals across Africa. Patients who are critically ill and in the ICU likely have a higher rate of infections, but as investigated by Tleyjeh et al, this rate is significantly higher among COVID-19 patients who were treated with the steroids or Tocilizumab.[20] Our patients have a statistically significantly higher rate of infection among patients receiving the Tocilizumab, which is consistent with the meta-analysis by the Tleyjeh group.[20] Clinicians need to have a low index of suspicion for superinfection infections in patients who receive Tocilizumab.

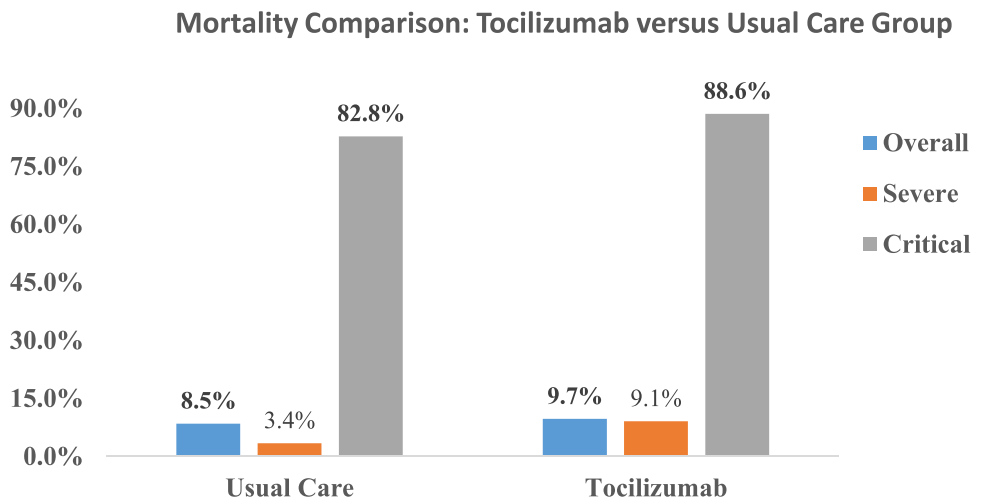

Figure 1 Mortality Comparison among patients receiving the Tocilizumab versus Usual care group (Overall, Severe COVID-19 and Critical COVID-19).

Table 4 Number and Site of Infection Among COVID-19 Patients

Infections from 55 Patients			
No of Infections	1	26	47.3%
	2	13	23.6%
	3	3	5.5%
	≥ 4	13	23.6%
Specimen	BLOOD	37	26.4%
	TRACHEAL ASPIRA	37	26.4%
	URINE	29	20.7%
	BRONCHIAL ASPIR	10	7.1%
	TISSUE	9	6.4%
	SPUTUM	7	5.0%
	WOUND SWAB	5	3.6%
	MISCELLANEOUS	4	2.9%
	CSF	1	0.7%
	PLEURAL FLUID	1	0.7%

Moreover, the incidence of bloodstream infection (BSI) remains a concern among patients who are critically ill and in ICU. Giacobbe and coworkers studied BSI among critically ill patients with COVID-19. They found the cumulative risk of BSI was 25% after 15 days and 50% after 30 days of ICU stay. They also found that anti-inflammatory agents such as steroids and Tocilizumab were associated with an increased risk of BSI with a hazard ratio of 1.07 and p=0.003.[38] In our patients, the BSI was 26.4% which is consistent with other studies.

Interestingly, the prevalence of HIV co-infection was low (2.3%), despite having a country HIV prevalence of 6%. There was no case of TB superinfection in both the Tocilizumab and non-Tocilizumab groups. This will help alleviate the anxiety of using Tocilizumab in Tuberculosis endemic countries where clinicians worry about having tuberculosis re-activation following Tocilizumab treatment.

The EMPACTA and CONVACTA trial looked at the safety information, including the infections rate. There was a significant difference in the infection rate between those studies and our study. It was 38.3%, 5.2%, and 17.2% in the CONVACATA, EMPACTA and our trial among patients in the Tocilizumab group, whereas 40.6%, 7.1% and 4.8% in the non-Tocilizumab groups.[15,16] In our trial, the infection rate among the patients taking Tocilizumab was much higher than the non-Tocilizumab group (17.2% vs 4.8%). As mentioned earlier that patients who received the Tocilizumab were more critical. Moreover, the high cost of the medication may have limited the usage of Tocilizumab in patients who were not critically ill.

There are several limitations of the study: variation in the admission guideline based on the Government regulation in the initial part of the study, small sample size, retrospective study, lack of information on which patients received steroids or anticoagulation therapy, radiological imaging data, variance in the usual care, lower female population, and the option to give the second dose of Tocilizumab based on clinical judgment with few preset parameters rather than the strict guideline. In addition, details regarding the patient's apache score between the Tocilizumab group and the non-Tocilizumab group were not available, which could demonstrate differences in mortality and infectious complications.

Table 5 Organism Incidence Among Patient Receiving Tocilizumab or Not

		Total (n=140)		Tocilizumab			
				No (n = 89)		Yes (n=51)	
Organism	Esch. coli	29	20.7%	17	19.1%	12	23.5%
	Ps. aeruginosa	18	12.9%	12	13.5%	6	11.8%
	Ent. cloacae	13	9.3%	6	6.7%	7	13.7%
	Aci. baumannii	11	7.9%	7	7.9%	4	7.8%
	K. pneumoniae	11	7.9%	6	6.7%	5	9.8%
	Staph. aureus	10	7.1%	4	4.5%	6	11.8%
	Entero. faecalis	9	6.4%	8	9.0%	1	2.0%
	C. auris	7	5.0%	5	5.6%	2	3.9%
	C. albicans	7	5.0%	5	5.6%	2	3.9%
	C. tropicalis	5	3.6%	5	5.6%	0	0.0%
	Staph. epidermidis	4	2.9%	3	3.4%	1	2.0%
	C. glabrata	3	2.1%	2	2.2%	1	2.0%
	Staph. haemolyticus	3	2.1%	1	1.1%	2	3.9%
	Staph. hominis	2	1.4%	2	2.2%	0	0.0%
	C. dubliniensis	1	0.7%	1	1.1%	0	0.0%
	C. lusitaniae	1	0.7%	0	0.0%	1	2.0%
	C. magnoliae	1	0.7%	1	1.1%	0	0.0%
	K. oxytoca	1	0.7%	1	1.1%	0	0.0%
	Ps. fluorescens	1	0.7%	1	1.1%	0	0.0%
	Salmonella group	1	0.7%	1	1.1%	0	0.0%
	Staph. warneri	1	0.7%	0	0.0%	1	2.0%
	Str. parasanguinis	1	0.7%	1	1.1%	0	0.0%

Conclusion

Tocilizumab was used in a select group of patients who had increasing oxygen requirements and worsening inflammatory markers. This is one of the first studies in Africa comparing infections in patients that received Tocilizumab versus the non-Tocilizumab group. Due to significant variation in the infection rates among the studies, a randomized control trial to assess the safety as it pertains to the superinfection and analysis of multiple superinfections needs to be studied in a diverse and minority population with different COVID-19 severities.

Disclosure

The authors report no conflicts of interest in this work.

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