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Interleukin-6 Trajectory and Secondary Infections in Mechanically Ventilated Patients With Coronavirus Disease 2019 Acute Respiratory Distress Syndrome Treated With Interleukin-6 Receptor Blocker

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OBJECTIVES: To describe the infectious complications and interleukin-6 trajectories in mechanically ventilated patients with coronavirus disease 2019.

DESIGN: Retrospective cohort study.

SETTING: ICUs at Washington University-Barnes Jewish Hospital in St. Louis, MO.

PARTICIPANTS: All consecutive patients admitted to the medical ICU and requiring mechanical ventilation from March 12, 2020, to April 21, 2020, were included.

INTERVENTIONS: Tocilizumab, an interleukin-6 receptor blocker, was prescribed at the discretion of the treating physicians to patients with a clinical picture compatible with cytokine release syndrome.

MEASUREMENTS: All the patients were followed to death or hospital discharge. Demographic and laboratory data were collected retrospectively from the electronic medical record. Interleukin-6 levels were measured at days 0, 3, 7, 14, and 21. Infections were divided into culture positive and culture negative (clinically suspected and treated). The main outcomes were infectious complications and interleukin-6 levels at different points in time.

RESULTS: Forty-three patients with respiratory failure secondary to coronavirus disease 2019 were on mechanical ventilation during the study period. Twenty-seven (68%) were male, and 31 (72.1%) were African-American. Median Charlson score was 2 (interquartile range, 0–4). Median Pao2/Fio2 was 171.5 (122–221) on the day of mechanical ventilation initiation, and 13 patients (30.2%) required vasopressors. C-reactive protein was 142.7 (97.7–213.7), d-dimer 1,621 (559–13,434), and Acute Physiology and Chronic Health Evaluation-II 11 (9–15). Interleukin-6 levels at admission were 61 pg/mL (interquartile range, 28.6–439 pg/mL). Patients treated with tocilizumab had higher levels of interleukin-6 at each measurement (days 0, 3, 7, 14, and 21) compared with patients receiving standard of care. Both groups reached peak interleukin-6 levels at day 7. Administration of tocilizumab was associated with a trend toward increased risk of infection.

CONCLUSIONS: Interleukin-6 levels peak at day 7 in patients with severe coronavirus disease 2019 pneumonia requiring mechanical ventilation

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and follows a similar trajectory in patients with coronavirus disease 2019 pneumonia requiring mechanical ventilation irrespective of treatment with interleukin-6R blockers. Interleukin-6 levels continued to rise in nonsurvivors, in comparison with survivors, where the rise in interleukin-6 levels was followed by a decline.

KEY WORDS: acute respiratory distress syndrome; coronavirus disease 2019; interleukin-6 receptor blocker; severe acute respiratory syndrome coronavirus 2

IMPORTANCE

Severe coronavirus disease 2019 (COVID-19) is characterized by pneumonia evolving into acute respiratory distress syndrome (ARDS) (1). In some patients, the respiratory failure worsens and is followed by shock and multiple organ failure, representative of the clinical picture seen during cytokine release syndrome (CRS) in patients receiving treatment with chimeric antigen receptor T cells (2). Drawing similarities between the two conditions and the elevated interleukin (IL)–6 levels in severe COVID-19 (3), IL-6 receptor blockade has been employed as an off-label therapeutic option in severe COVID-19 pneumonia (4).

Clinical criteria—which overlap with sepsis—are routinely used to initiate treatment with IL-6 inhibitors for CRS (5) and have been applied to severe COVID-19. However, whether or not the inflammatory response during severe COVID-19 overlaps sufficiently with classical CRS to the point that IL-6 receptor blocking therapy will have similar benefits remains to be fully determined (6). Retrospective studies hint at improved outcomes with the use of tocilizumab (IL-6 receptor blocker) (7–10). However, preliminary results from randomized controlled trials are not as promising (11, 12).

One noteworthy consequence of IL-6 receptor blockade is the development of secondary infections (13). In respiratory viral infections resulting in ARDS such as influenza, secondary bacterial infections are common, and the dysregulated immune response augments their frequency (14). Bacterial pneumonia was thought to be the predominant cause of death in the 1918 influenza pandemic, and it was responsible for approximately 30% of the deaths during the more recent H1N1 2009 pandemic (15, 16). Previous experience with IL-6 receptor blockers is mixed, with increased rates of infections in patients with rheumatologic disease but similar rates in those with CRS when compared with similar patients on alternative treatment regimens (13, 17).

OBJECTIVES

We describe the IL-6 trajectory in survivors and nonsurvivors among patients receiving IL-6 receptor blockers plus standard of care versus standard of care alone. Given the competing risks for bacterial superinfections, we also set out to characterize the impact of tocilizumab on infection rates in patients with severe COVID-19–related pneumonia.

DESIGN, SETTING, AND PARTICIPANTS

This retrospective cohort study was conducted at Barnes Jewish Hospital-Washington University School of Medicine in St Louis, MO, a tertiary academic center with 1,250 beds. All consecutive patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) requiring mechanical ventilation from March 12, 2020, to April 21, 2020, were included in the analysis. Tocilizumab was prescribed at the discretion of the treating physicians. Patients with suspected CRS (5) were considered for treatment if they had temperature greater than or equal to 38°C, hypotension requiring vasopressors, and rising C- reactive protein (CRP) levels at a rate concerning to the treating physician. Patients received 8 mg/kg with the possibility of a second dose at 12–24 hours later, if the clinical circumstances persisted. The Institutional Review Board (IRB) at Washington University School of Medicine approved the study protocol (IRB ID: 202006151) and waived the need for informed consent.

MAIN OUTCOMES AND MEASURES

The main outcomes of the study were IL-6 levels and infection rates. Mortality was included as a secondary outcome. Comparisons were described between patients receiving tocilizumab and those who did not. Continuous variables were reported as median and interquartile range (IQR), categorical variables were compared using the Fisher exact test. We separated infections into culture proven and clinically

suspected infections when patients developed new signs of sepsis (suspicion of infection as evidenced by blood cultures and administration of at least 4 d of systemic antibiotics and new organ dysfunction) (18). Infectious workup including cultures were obtained at the discretion of the treating physician and based on clinical suspicion for infection. For respiratory viruses other than SARS-Co-V2 and for intracellular pathogens (e.g., *Bordetella* species, *Mycoplasma* species), we used Biofire Diagnostics Film Array respiratory panel (Biofire Diagnostics, Murray, UT). Logistic regression was used to ascertain the relationship between predictors and non–COVID-19 infections or mortality at 30 days. Given the small sample size, the multivariable logistic regression was limited to two variables defined a priori: Acute Physiology and Chronic Health Evaluation-II score and tocilizumab administration.

Comorbidities, demographic, and laboratory data were abstracted from the electronic medical record the first 24 hours of ICU admission, and on day 5, the median time to tocilizumab administration. IL-6 levels were measured on stored plasma specimens drawn at admission to the ICU (considered day 0) and on days 3, 7, 14, 21, and 28, and the results were not available to the treating physician. The cytokine levels were obtained using a Luminex assay panel (Cytokine 35-Plex Human Panel; Thermo Fisher Scientific, Waltham, MA).

RESULTS

A total of 43 patients required mechanical ventilation from March 21, 2020, to April 21, 2020. Twelve received treatment with tocilizumab, with one patient receiving two doses. Both groups are compared in **Table 1**. The cohort was predominantly male (62.8%) and of African American race (81.4%). Median APACHE-II score was 11 (IQR, 9–15). Mechanical ventilation was administered for 12.5 days (IQR, 7–18 d), and the median length of stay was 21.5 days (IQR, 11–38 d). Twenty-three patients (53.5%) developed at least one secondary infection, and 20 (47.5%) died within 30 days.

The clinical characteristics of the two groups did not differ significantly at baseline (Table 1). At day 5, median time to tocilizumab administration, CRP was significantly higher in patients treated with tocilizumab (Table 1), the same relationship was true for absolute neutrophil to lymphocyte count ratio. Lower Pao_2/Fio_2 (odds ratio [OR], 0.98; CI,0.97–0.99; $p = 0.043$) and higher CRP (OR, 1.01; CI, 1.01–1.03; $p = 0.026$) at admission were associated with tocilizumab administration. The median time from hospital admission to ICU was 0 days (IQR, 0–2.5 d) in the tocilizumab group and 0 days (IQR, 0–2 d) in the standard treatment, p value equals to 0.811. All the patients with refractory hypoxemia on high-flow nasal cannula transitioned directly to invasive mechanical ventilation. The median number of hours to mechanical ventilation after arrival to the ICU was 1 hour (IQR, 1–5.5 hr) in the tocilizumab group and 0 hours (0–2 hr) in the standard of care group, p value equals to 0.956. IL-6 levels were measured at least once in 16 patients, and 15 patients had at least three consecutive measurements at 0, 3, and 7 days. At admission, IL-6 levels were higher in both groups compared with healthy uninfected controls (61 [IQR, 28.6–439.2] vs 5.9 pg/mL (IQR, 3.6–20.2 pg/mL]; $p < 0.01$). At all measurement points (days 0, 3, 7, 14), patients treated with tocilizumab had higher IL-6 levels than patients receiving standard of care (day 0: 297 vs 31.7 pg/mL, day 3: 546.5 vs 160.6 pg/mL, day 7: 209.7 vs 370.8 pg/mL, day 14: 825.7 vs 65.7 pg/mL; $p < 0.01$). IL-6 levels peaked at day 7 in both groups. The trajectory differentiated survivors from nonsurvivors: by day 14, survivors had declining IL-6 levels in both treatment groups (**Fig. 1**), whereas nonsurvivors did not.

Secondary infections were common in both groups (Table 1). The median time to the first culture-positive infection since admission to the ICU was 9.8 days (IQR, 2–12.8 d). From admission to discharge, 23 patients experienced 11 episodes of culture-negative sepsis, 18 episodes of bacteremia (**Table 2**), 12 bacterial and one fungal pneumonia (**Table 3**), five urinary tract infections, and two skin and soft-tissue culture-positive infectious episodes. Twelve bloodstream infections (66.6%) and seven episodes of pneumonia (53.8%) were attributed to Gram-positive cocci (GPC). For the first 72 hours after admission, the majority of isolated microorganisms were also GPC (7/8; 87.5%). *Clostridium difficile* colitis was noted in one patient in each group. Additionally, we counted three coinfections with respiratory viruses, and a coinfection with *Cryptococcus neoformans*. Forty-two of 53 infections (79.2%) were diagnosed after 5 days in the ICU. There were no significant differences in the distribution of pathogens between the two groups ($p = 0.75$). In univariate analysis, there was a trend toward higher risk of any clinically diagnosed infection in patients receiving

TABLE 1.

Mechanically Ventilated Patients for Severe Coronavirus Disease 2019–Related Pneumonia Treated With Tocilizumab or Standard of Care

Variables	Tocilizumab, *n* = 12	Standard Care, *n* = 31	*p*
Age, yr, median (interquartile range)	60 (56–67)	69 (60–78)	0.12
Male, *n* (%)	3 (25)	13 (41.9)	0.484
Race, *n* (%)			0.133
White	4 (33.3)	4 (12.9)	
African American	6 (50)	25 (80.7)	
Other	2 (16.7)	2 (6.5)	
Body mass index (kg/m^2), median (interquartile range), *n* (%)	29.5 (28–37.7)	32.4 (28.3–35)	0.856
Diabetes mellitus, type 2, *n* (%)	3 (25)	9 (29.03)	1
Chronic kidney disease, *n* (%)	5 (41.7)	12 (38.7)	1
Congestive heart failure, *n* (%)	2 (16.7)	9 (29)	0.698
Charlson score, median (interquartile range)	0 (0–3)	2 (0–4)	0.125
Pao_2/Fio_2 at admission, median (interquartile range)	139 (103–173.5)	179 (114–256)	0.057
Shock at admission, *n* (%)	3 (25)	10 (32.3)	0.727
C-reactive protein at admission[a], median (interquartile range)	198.1(150.6–315)	127.9 (84.8–213.7)	0.094
C-reactive protein at 5 d from admission (mg/dL)[a], median (interquartile range)	280 (264.1–308.8)	184 (93.1–277.1)	0.008
Ferritin at admission[b], median (interquartile range)	2,903 (584–3,291)	873 (532–1,526)	0.315
Ferritin at 5 d from admission[b], median (interquartile range)	1,473 (795–3,473)	1,303 (704–2,159)	0.592
D-dimer on admission[b], median (interquartile range)	663.5 (434–893)	1,834 (603–13,507)	0.261
D-dimer at 5 d from admission[b], median (interquartile range)	3,490.5 (1,213–5,451)	4,551.5 (1,495–15,685)	0.644
Interleukin-6 (pg/mL)[c], median (interquartile range)	166.8 (55–739.7)	48 (26–512.5)	0.205
Chest radiograph acute lung injury score[d], *n* (%)			0.698
< 2	2 (16.7)	8 (25.8)	
≥ 2	10 (83.3)	23 (74.2)	
Absolute neutrophil to lymphocyte count ratio at admission, median (interquartile range)	10.3 (4.8–16.7)	7.2 (4.8–14.5)	0.417
Absolute neutrophil to lymphocyte count at 5 d from admission, median (interquartile range)	14.2 (7.5–34.5)	7.6 (6–12)	0.059
Acute Physiologic Assessment and Chronic Health Evaluation-II score, median (interquartile range)	12 (10.5–16.5)	11 (8–15)	0.202

(*Continued*)

TABLE 1. (*Continued*).
Mechanically Ventilated Patients for Severe Coronavirus Disease 2019–Related Pneumonia Treated With Tocilizumab or Standard of Care

Variables	Tocilizumab, *n* = 12	Standard Care, *n* = 31	*p*
Culture-negative sepsis, *n* (%)	5 (41.7)	6 (19.4)	0.241
Any sepsis, *n* (%)	9 (75)	14 (45.2)	0.099
Length of mechanical ventilation, d, median (interquartile range)	13.5 (11.5–18)	10 (5–18)	0.154
Length of stay, d, median (interquartile range)	23.5 (19.5–38)	16 (8–35)	0.273
Mortality at 30 d, *n* (%)	3 (25)	17 (56.7)	0.091

[a]C-reactive protein in mg/dL.
[b]Ferritin and D-dimer expressed as µg/L.
[c]Interleukin-6 levels at admission to the ICU available for 16 of 43 patients.
[d]Acute Lung Injury score: 0 if clear, 1–4 according to the number of quadrants involved.

tocilizumab (OR, 3.6; CI, 0.82–16.1; $p = 0.088$) as well as for culture-positive bacteremia or pneumonia (OR, 4.1; CI, 0.99–17.6; $p = 0.052$). APACHE-II score was associated with increased mortality in uni- and multivariable analyses (OR, 1.22 [95% CI, 1.02–1.46]; $p = 0.029$), and tocilizumab administration was a significant predictor of survival (OR, 0.15 [95% CI, 0.03–0.83]; $p = 0.03$). Elapsed number of days from admission to the ICU to administration of tocilizumab did not influence mortality (OR, 0.93 [CI, 0.62–1.39; $p = 0.715$]. A sensitivity analysis excluding patients dying within 48 hours of admission did not significantly change the results.

CONCLUSIONS AND RELEVANCE

In our cohort, IL-6 levels followed a similar trajectory for the survivors of severe COVID-19 ARDS requiring mechanical ventilation irrespective of tocilizumab administration with an initial rise followed by declining levels. IL-6 levels continued to rise in nonsurvivors after day 7. Additionally, treatment with an IL-6 receptor blocker was associated with an increased risk of nosocomial infections and improved survival after adjusting for severity of critical illness.

IL-6 Levels and Trajectory

Compared with historical ARDS cohorts, patients with severe COVID-19 pneumonia had lower initial IL-6 levels (19, 20), but these continued to increase on subsequent measurements. It is still unclear whether death occurs due to uncontrolled viral replication, an uncontrolled, viral-independent immune-inflammatory response similar to CRS or a different process (21, 22).

Several studies have reported single IL-6 measurements on the day of hospital admission. Levels were only mildly elevated with median levels ranging from 11 to 26 pg/mL (23–25). These levels are significantly lower than median measurements in previous ARDS cohorts which ranged from 130 to 443 pg/mL for hypoinflammatory cases and between 578 and 1,618 pg/mL in hyperinflammatory ARDS (19, 20). Our cohort only included critically ill patients, many of them on mechanical ventilation at admission to the hospital. Even though initial IL-6 levels were in line with hypoinflammatory ARDS, by day 7–10, IL-6 levels rose reaching hyperinflammatory ARDS levels.

This late rise in IL-6 levels has been described in other cohorts and correlates with the clinical presentation of patients. In an analysis of 113 patients with COVID-19 including 33 severe cases, the highest registered IL-6 levels were measured 10 days after the onset of symptoms (26). In a related analysis of a subset of these patients, IL-6 levels also showed an initial expected rise after the administration of an IL-6 receptor antagonist. Although initial IL-6 levels were not predictive of the outcome, the highest level of IL-6 was associated with severe disease (7).

Subphenotyping patients with ARDS based on inflammatory markers has been associated with better response

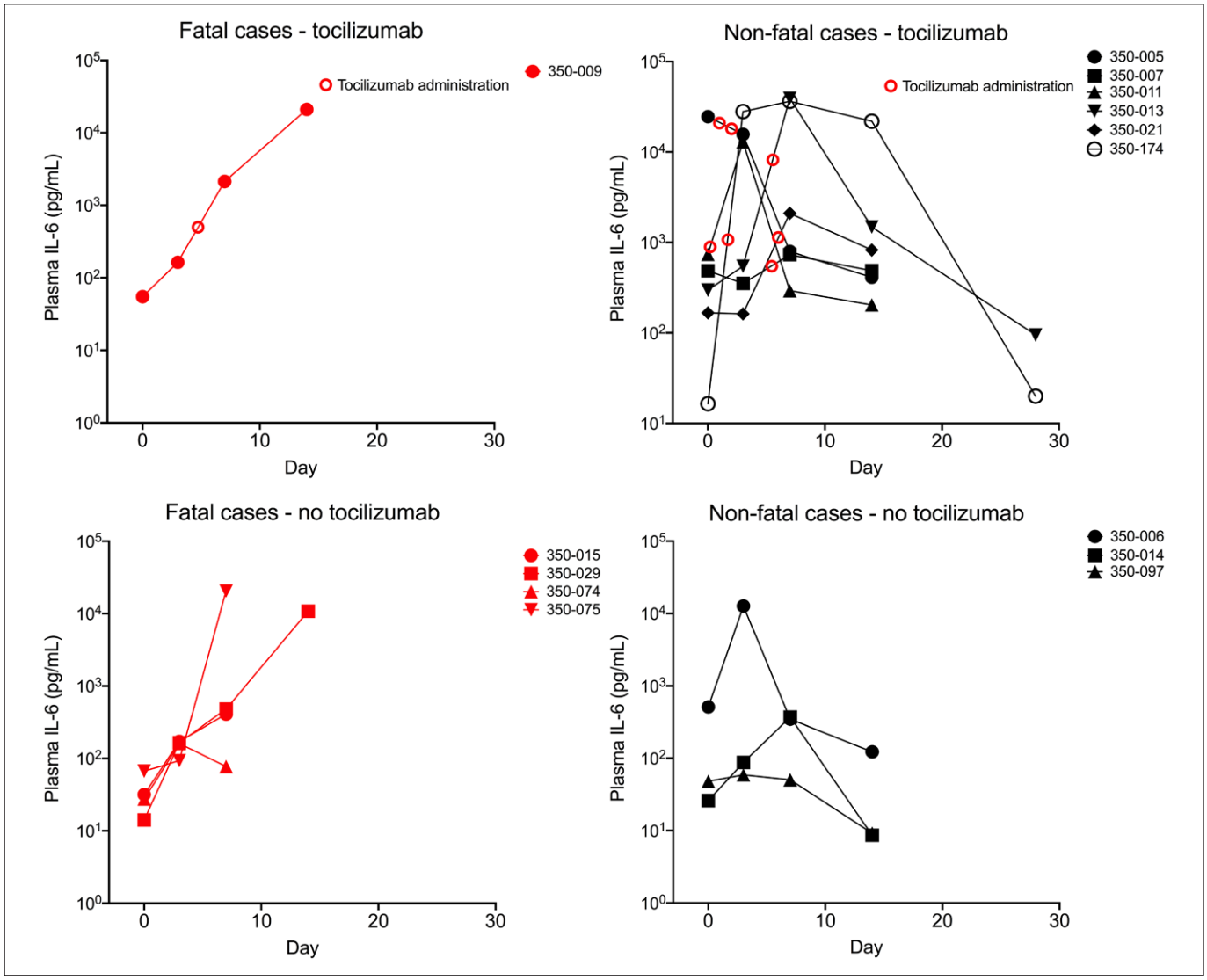

Figure 1. Trajectory of interleukin-6 levels for each of the 16 patients with measurements overtime. The figure is subdivided into four panels according to Tocilizumab administration and survival at 30 d. Measurements were performed at 0, 3, 7, 14, 21, and 28. Each patient is identified by a six-digit code and a symbol. The timing of tocilizumab administration for each patient is represented by a red circumference on his/her trajectory line. IL-6 = interleukin-6.

to anti-inflammatory therapies in secondary analyses of several randomized controlled trials (19, 20). In the case of viral pneumonia secondary to SARS-CoV-2, with its protracted clinical course, the inflammatory phenotype becomes evident later in the disease process. Future studies should evaluate whether the slope or velocity of rise in cytokines is better associated with response to IL-6 receptor blockers or other anti-inflammatory agents.

The recently published Randomized Evaluation of COVID 19 Therapy study evaluated the use of dexamethasone 6 mg/d for up to 10 days (27). Their results provide indirect evidence supporting a role for anti-inflammatory therapy for a subset of patients. Treatment resulted in an overall reduction in mortality of 15% among patients requiring any form of respiratory support. There was, however, a trend toward higher mortality in treated cases not requiring oxygen. Patients requiring respiratory support have consistently been recognized as having higher IL-6 levels and other inflammatory markers (7, 24, 28). The continued rise in these markers along with hypoxemia could be used to refined the selection of patients for treatment.

Infectious Complications

Respiratory viruses affect the innate and adaptive response to bacterial pathogens (14). Clinical observations of the association between viral infections and

TABLE 2.
Etiological Agents of Bacteremia

Pathogen	Tocilizumab, *n* (%)	Standard, *n* (%)
Candida parapsilosis	0	1 (3.2)
Clostridium perfringens	0	1 (3.2)
Coagulase-negative Staphylococci	0	5 (16.1)
Staphylococcus aureus	1 (8.33)	1 (3.2)
Streptococcus viridians	2 (16.7)	2 (6.5)
Enterobacter cloacae and S. epidermidis	0	1 (3.2)
Prevotella melaninogenica	0	1 (3.2)

For common contaminants, two positive blood cultures from different sites and a syndrome compatible with infection were required. Three patients had a second episode of bacteremia, one with *Prevotella melaninogenica*, one with *S. epidermidis*, and one with *S. aureus*.

TABLE 3.
Etiologic Agents of Pneumonia

Pathogen	Tocilizumab, *n* (%)	Standard, *n* (%)
Cryptococcus neoformans	0	1 (3.2)
Chlamydophila pneumonia	0	1 (3.2)
Enterobacter cloacae	1 (8.3)	0
Moraxella catarrhalis	0	1 (3.2)
Staphylococcus aureus	3 (25)	3 (9.7)
Streptococcus pneumonia	0	1 (3.2)
Stenotrophomonas maltophilia	0	1 (3.2)
Adenovirus	0	1 (3.2)
Coronavirus HKU1	0	1 (3.2)

Viruses were recovered from nasopharyngeal swabs and bacteria and fungi from lower respiratory tract samples (tracheal aspirates and bronchoalveolar lavage) in patients with clinical syndromes compatible with pneumonia.

bacterial pneumonia date back to influenza epidemics in the 19th century (29). During the 2009 H1N1 influenza epidemic, 35% of the deaths were ascribed to bacterial complications (30). Middle eastern respiratory virus resulted in bacterial complications in cohorts not treated preemptively with antibiotics (31). When coinfected, GPC, in particular, *Streptococcus pneumoniae* and *Staphylococcus aureus* are responsible for greater than 50% of these cases, with a variety of other pathogens accounting for the rest (15). Additionally, the need for mechanical ventilation and invasive procedures also increases the risk of nosocomial infections. To that accord, the data regarding the infectious risk of tocilizumab therapy are mixed (13, 17). In our cohort, bacterial coinfections were frequent and a preponderance of GPC as pathogenic organisms was detected at all times during the ICU stay. Although it did not reach statistical significance, there was a trend toward higher rates of clinically diagnosed and culture-positive infections in the group of patients receiving tocilizumab.

When used in patients with rheumatologic disorders, tocilizumab (8 mg/kg dose) is associated with a greater risk of infection) (13). For patients with CRS following chimeric antigen receptor (CAR) T cell therapy, data are limited, but infection rates are similar to CRS not treated with tocilizumab (17). These differences might be related to: 1) the long duration of treatment in patients with rheumatologic disorders, often multiple years, and 2) the profound immune dysregulation of oncologic patients undergoing treatment with CAR T cells, with tocilizumab having little additive effect in the pretest probability of infectious complications.

In a COVID-19 Italian cohort of 544 patients with severe disease, patients treated with tocilizumab-treated patients had a rate of infection, three times higher than controls (13% vs 4%; $p < 0.001$) (28). Another study from Brooklyn, New York found the opposite, with a higher incidence of bacteremia in the control group of their case control study (23.7 % vs 12.5%; $p = 0.04$) (32). Price et al (7) reported an incidence of bacteremia in only 4% in their cohort of 153 patients treated with tocilizumab. The apparent discordance between studies could be related to diverse treatment strategies, infection definitions, adjunctive use of other immunomodulators, and the lack of a standard measure to evaluate the severity of COVID-19 (33).

Our study has several limitations. First, the sample size is small. This is in part related to the increased risk of infections we observed in our initial experience, after which we were cautious about using IL-6 receptor blockade outside of the purview of clinical trials. We

hope that by sharing our results, more clarity regarding the risks and benefits of IL-6 receptor blockade therapy can be gained over time. Second, although we provide longitudinal measurements of IL-6, the true day 0, the day the infection was acquired is unknown. This problem is common in critically ill patients admitted to the ICU with ARDS. Third, we do not have data on concurrent viral load to parallel IL-6 levels and are hence unable to determine why there was such a difference between survivors and nonsurvivors regardless of tocilizumab use.

In conclusion, we hope the observational data presented will help to evaluate and design future studies of immune modulators in viral pneumonia. Although we await, clinicians should exercise caution with off-label drug use.

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Drs. Vazquez Guillamet and Guillamet performed the statistical analyses and drafted the final article. All authors contributed to the conception, data acquisition, the critical interpretation of the results, and of the final article. All authors take responsibility for the accuracy of the data herein presented.

This study was conducted in accordance with the amended Declaration of Helsinki. Local institutional review boards or independent ethics committees approved the protocol. Informed consent was waived by the Institutional Review Board (IRB) for this cohort study. Subject IRB:202003154-005493516246649.

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