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Survival Benefit of Tocilizumab in COVID-19 May Be Greater in Patients with Higher Measured Interleukin 6 Levels

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Abstract: The interleukin 6 (IL-6) receptor-blocking antibody tocilizumab was repurposed in the coronavirus pandemic with the intention of blocking the excess inflammatory activation associated with severe disease. We retrospectively evaluated the response to tocilizumab based on measured levels of IL-6 as well as other inflammatory markers. In the sample of 41 patients with measured levels, 16 received tocilizumab. In the patients who received tocilizumab, there was a statistically significant relationship between both higher IL-6 levels and measured acute phase reactants with mortality, but not in those who did not. Additionally, an improved mortality after tocilizumab was suggested with those with higher IL-6 measurements, but not in those with lower levels, but this finding failed to achieve statistical significance ($p = 0.14$). Though this study is limited by a small sample size and retrospective design, an association is suggested between higher IL-6 levels and improved mortality after tocilizumab.

Keywords: coronavirus; COVID; tocilizumab; interleukin 6; cytokine

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1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2, COVID-19, COVID) was first identified and reported to the World Health Organization (WHO) after an outbreak in December, 2019 in Wuhan, China. This virus subsequently spread across the entire globe, burgeoning into a pandemic that has become the most disruptive public health crisis in a century. At the time of writing, there have been over 242 million documented cases of SARS-CoV-2, and nearly 5 million deaths [1,2].

COVID-19 most commonly causes a respiratory infection that can range from mild to severe acute respiratory distress syndrome (ARDS) [3]. In addition, gastrointestinal syndromes have been reported as well as a post-infectious syndrome or post-COVID-syndrome that can cause prolonged fatigue, anosmia, and respiratory symptoms [4,5]. One of the more striking effects of acute SARS-CoV-2 infection has been a profound inflammatory response, first reported in February, 2020, that includes a spectrum of cytokine release syndromes including cytokine storm, macrophage activation syndrome (MAS), and hemophagocytic lymphohistiocytosis (HLH) [6–9].

Both the innate and adaptive immune systems have cellular and humoral components. The adaptive system is comprised of B cells and the antibodies they produce, as well as cytotoxic and helper T cells, while the innate system is comprised of numerous cell types including macrophages, natural killer cells, and neutrophils, along with the humoral complement system. Both are potent activators of the inflammatory cascade (Figure 1) [10].

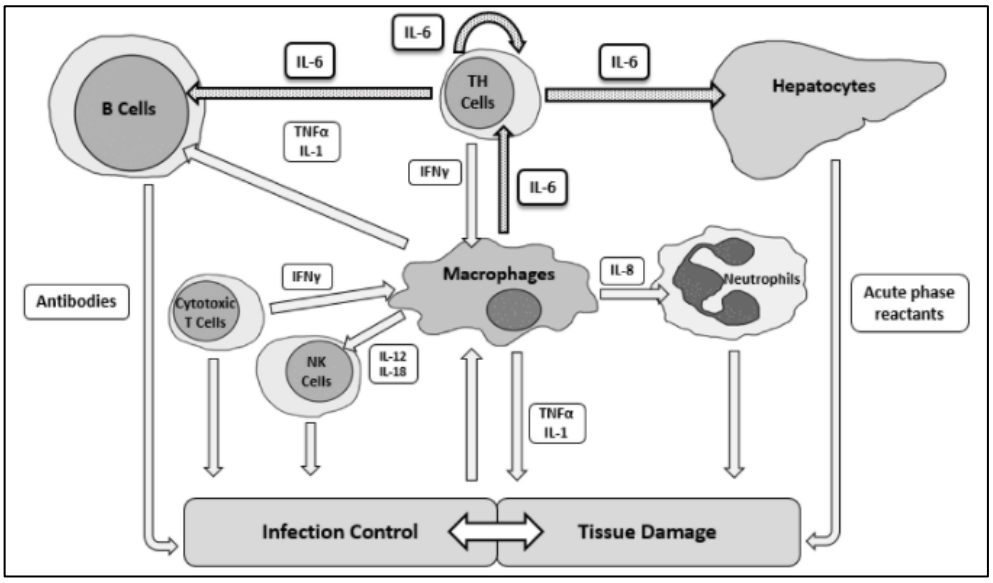

Figure 1. Major cytokine activation within the inflammatory cascade with attention to the multiple roles of IL-6 in directly and indirectly in promoting the proinflammatory response in relation to other major cytokines including IL-1, IL-8, IL-12, IL-18, interferon gamma (IFNy) and tumor necrosis factor alpha (TNFa).

When the body becomes exposed to a foreign material, initially neutrophils and macrophages, and later TH1 and CD4 cells, respond by releasing proinflammatory cytokines including tumor necrosis factor α (TNFα), interleukin-1 (IL-1), and IL-6, IL-8, and interferon γ (IFNγ) [10]. This inflammation produces typical inflammatory symptoms such as fevers, chills, aches, anorexia, and fatigue, and when extreme can also include vasodilation and permeability, extravasation of fluid, a prothrombotic state, cardioplegia, and direct tissue injury. This reactive response is balanced by concomitant release of anti-inflammatory cytokines including IL-10, IL-12, IL-22, and transforming growth factor beta (TGFß) [10]. Excessive inflammatory syndromes are the result of an excess of proinflammatory activation relative to the anti-inflammatory response [10]. This imbalance can lead to multiorgan dysfunction and failure if not appropriately treated, and patients can decompensate rapidly, causing hypotension, coagulopathy, shock, and death [6,11].

One of the key cytokines in the inflammatory cascade is IL-6, the primary inducer of acute phase reactant protein synthesis [12]. Measuring and trending specific acute phase reactants have been used in diagnosis, assessment of therapeutic response, and prognosis in SARS-CoV-2 [13,14]. These nonspecific inflammatory markers are uniformly elevated in severe disease and include, among others, C-reactive protein (CRP), ferritin, D-dimer, and lactate dehydrogenase (LDH) [13].

IL-6 has been a focus of significant interest in COVID-19 due to the high degree of inflammatory activation, and extremely elevated levels have been reported. A systematic review of the existing literature on the subject by Coomes and Haghbayan concluded that IL-6 levels were particularly elevated in patients with severe COVID-19 disease [15]. It was found that these elevated levels were associated with adverse clinical outcomes such as severity of illness, need for intensive care unit admission, need for mechanical ventilation, ARDS, and death [13,15]. Despite these data, others also found that levels of cytokines including IL-6 were not as elevated in COVID-19 patients as would be expected based on the severity of their symptoms, casting doubt on the importance of IL-6 in the pathogenesis of the disease [16].

Nevertheless, IL-6 garnered additional attention due to the preexistence of a medication, tocilizumab, that blocks its receptor, previously approved by the Food and Drug Administration for the treatment of rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and cytokine-release

syndrome [3,17]. It was among a number of drugs that were considered for repurposing in the early pandemic. Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor, which prevents activation by IL-6 [3]. Given the mechanism of action, it was felt that this treatment might help to blunt the excessive inflammatory damage in COVID-19 and result in improved morbidity and mortality, a theory that has so far been borne out by several randomized control trials and when assessed in meta-analysis [3].

However, prior to the publication of these studies, inconsistencies in reporting resulted in an absence of clarity, and additional early efforts were made to understand the effects and potential role of tocilizumab in the treatment of COVID-19. One such effort, presented here, is a small retrospective cohort of patients for whom both measured IL-6 levels and tocilizumab administration data were obtained from a small community hospital in the first six-months of the pandemic.

2. Materials and Methods

2.1. Design

Data for this analysis were taken from a de-identified data set that was gathered as part of a quality control project at a single New York Metropolitan area non-academic community hospital. At the time of collection, each patient's data were assigned a random identifier and no protected health information was included in the dataset. This de-identified dataset was then examined later for this analysis.

The study design and data were reviewed with the institutional Review Board of New York University Langone Health system and were determined not to require review or waiver.

2.2. Inclusion Criteria

Inclusion into the set was defined by any and all patients with the diagnosis of COVID-19 admitted to the facility between the dates of March 1st and May 30th, 2020 who also had cytokine panels or IL-6 levels collected The decision to send IL-6 levels was based on the treating providers' judgement and was in no way related to data collection. Similarly, the decision to administer tocilizumab was made by the provider teams, which at this hospital during this time period required the decision of the primary provider as well as subsequent approval by the infectious disease service and the Chief of Medicine prior to administration. The original dataset was collected in the month following the last value (June, 2020) and represented all COVID-19 patients admitted to the facility up to that point. Exclusion criterion was failure to meet the above conditions.

2.3. Collected Data

The data collected for the set included the age and sex of the individuals, whether or not they had received tocilizumab, and whether they required ventilatory support (including days on the ventilator), or renal replacement therapy. Laboratory analyses included IL-6 levels (by immunoassay, reference < 5.00 pg/mL), as well as CRP (by immunoturbidimetric assay, reference < 8.0 mg/L), D-dimer (by immunoturbidimetric assay, reference < 500 ng/mL), and LDH (by spectrophotometry, reference 120–250 U/L) levels. Dispositions were recorded as discharged, transferred, or expired. No additional therapies or interventions including non-invasive ventilation, administration of steroids, hydroxychloroquine, or antibiotics were recorded in the dataset. Antiviral medications such as remdesivir or monoclonal antibodies were not yet available at this facility.

2.4. Data Analysis

These data were tabulated and analyzed to assess if there was an association between the effect of tocilizumab administration on mortality and laboratory analyses of IL-6, CRP, LDH, or D-dimer levels. SPSS version for Windows/Mac, version 26.0 for Windows/Mac (IBM Corp., Armonk, NY, USA) was used for data analysis. Distributions of the marker data were plotted. With a small number of low outliers removed, CRP showed a normal

distribution with a small positive skew. D-dimers showed a bimodal distribution with peaks at 1170 and 23,200 ng/mL; LDH showed a normal distribution with a large positive skew. Similarly, IL-6 levels across all the groups showed a normal distribution with a large positive skew. Post hoc test with one way ANOVA were performed for multiple comparisons between each value to mortality in groups with and without tocilizumab. Cross tabulation and bivariate analyses were performed using Fisher's exact test with all combinations of the above factors. Odds ratios (OR), 95% confidence intervals (CI), and *p*-values were reported as appropriate. In addition, one way analysis of variance was performed to assess the significance of the peak biomarker values with mortality. Traditional Kaplan–Meier analyses could not be performed due to the absence of temporal data and small number of patients.

3. Results

In the analyzed dataset, there were 41 patients, in whom IL-6 levels were assessed during the designated period of review. Of these 41, 16 received tocilizumab. The overall mortality rate for the group was 51%. A total of 66% were male, and 48% were over 60 years of age. Additional characteristics are given in Table 1.

Table 1. Characteristics of survivors and non-survivors.

Category	Survivors (%)	Non-Survivors (%)	Total (%)
Male	14 (70)	13 (62)	27 (66)
Female	6 (30)	8 (38)	14 (34)
Age < 40	5 (25)	0 (0)	5 (12)
Age 40–60	9 (45)	7 (33)	16 (39)
Age > 60	6 (30)	14 (67)	20 (49)
Tocilizumab	8 (40)	8 (38)	16 (39)
Mechanical Ventilation	7 (35)	17 (81)	24 (59)
Renal Replacement	2 (10)	10 (48)	12 (29)
Admitted in March	4 (20)	6 (29)	10 (24)
Admitted in April	11 (55)	10 (48)	21 (51)
Admitted in May	5 (25)	5 (24)	10 (24)

General characteristics of this group that were not found to be associated with survival included sex ($p = 0.74$, OR = 1.44, CI = 0.39–5.27) and month of admission (March versus May) ($p = 0.65$ OR = 0.67 CI = 0.11–3.92). Clinical characteristics that achieved a statistically significant association with increased mortality included ventilator use ($p < 0.01$, OR = 0.13, CI = 0.03–0.53), and renal replacement therapy (RRT) ($p = 0.02$, OR = 0.12 CI = 0.02–0.67), and age ($p < 0.01$).

Measured IL-6 levels were extremely variable within the group. A total of 15 patients measured below the threshold for detection (normal: < 10 pg/mL), and positive values as high as 2709 pg/mL were reported with an overall mean elevation of 240 pg/mL and a median of 14 pg/mL. Levels of inflammatory markers showed less variation, but still a positively skewed distribution. Both CRP and D dimer levels were strongly associated with mortality in a statistically significant way (CRP $p = 0.02$, D dimer $p = 0.04$). LDH levels were associated with mortality, but in this sample, failed to reach statistical significance ($p = 0.24$). Additional values are given in Tables 2 and 3.

Table 2. Biomarkers in survivors and non-survivors.

Lab Value	Survivors	Non-Survivors	Overall	Significance
CRP (mg/L)				
Mean	19.4	29.6	24.7	$p = 0.02$
Median	26.5	29.0	26.5	
D-dimer (ng/mL)				
Mean	4097	10894	7757	$p = 0.04$
Median	755	5417	2997	
LDH (U/L)				
Mean	1278	6139	3830	$p = 0.24$
Median	1175	2205	1716	
IL-6 (pg/mL)				
Mean	171	309	247	$p = 0.40$
Median	5	106	16	

Table 3. Biomarkers and survival in the tocilizumab and non-tocilizumab groups.

Lab Value	Tocilizumab	Non-Tocilizumab	Significance
CRP (mg/L)			
Mean	28.8	27.5	$p = 0.07$
Median	20.8	20.0	
D-dimer (ng/mL)			
Mean	7471	4837	$p = 0.89$
Median	7956	2507	
LDH (U/L)			
Mean	2257	1647	$p = 0.22$
Median	1747	1204	
IL-6 (pg/mL)			
Mean	348	182	$p = 0.34$
Median	46	12	

Among patients who did not receive tocilizumab, IL-6 levels less than three times the upper limit of normal (>30 pg/mL) were associated with lower mortality in a statistically significant way ($p = 0.02$, OR = 0.11 CI = 0.02–0.72). Among patients who did receive tocilizumab, there was no association identified between mortality in those with higher or lower IL-6 levels. In the group with IL-6 levels greater than three times the upper limit of normal, there was a trend toward improved mortality with tocilizumab that failed to achieve statistical significance ($p = 0.14$). In the group with IL-6 levels less than this threshold, there was no association.

All three of the additional biomarkers collected showed a statistically significant inverse relationship with survival (CRP: $p = 0.02$, D dimer: $p = 0.03$, LDH: $p < 0.01$) in the group not treated with tocilizumab. Among patients who did receive tocilizumab, none of these markers bore a statistically significant relationship to survival (CRP: $p = 0.41$, D dimer: $p = 0.70$, LDH: $p = 0.14$).

Administration of tocilizumab was not statistically significantly associated with a change in mortality in either patients found to have higher or lower CRP levels ($p = 0.22$, $p = 0.87$, respectively), LDH levels ($p = 0.22$, $p = 0.83$, respectively) or D dimer ($p = 0.45$, $p = 0.90$, respectively). When considering all patients with interleukin levels assessed, the study did not identify an association between administration of tocilizumab and increased survival ($p = 0.90$, OR = 1.08 CI = 0.31–3.80).

4. Discussion

IL-6 is considered to be one of the most important cytokines promoting the inflammatory response and medications designed to interrupt its signaling have previously been used to treat disease processes with a high degree of inflammation [18]. Due to the high degree of inflammation that occurs during acute COVID-19 infection and the pre-existence of an agent targeting this pathway, tocilizumab was considered to be a promising potential medication for repurposing [19].

During the period of data collection here, data evaluating efficacy were not yet available. Since this time, correlations between IL-6 levels, severity of disease, and outcomes have been reported in multiple prior studies [20,21]. Data collected from the same period as the dataset presented here showed that a decrease in IL-6 on repeated measurement correlated with survival [22]. Interestingly, however, another study showed that IL-6 levels rose in patients after administration of tocilizumab in both survivors and non-survivors [23]. One early study which examined tocilizumab showed that IL-6 levels greater than 37.54 pg/mL were highly predictive of death overall, but that this association was not present after tocilizumab administration suggesting a protective effect [24].

The data presented here failed to corroborate this relationship to a statistically significant degree but did, unsurprisingly, show a trend toward a protective effect of tocilizumab in those with elevated IL-6 levels. The absence of this trend in subjects without elevated measured IL-6 levels suggests that any benefit may be limited to those in whom an excessive IL-6 driven proinflammatory response may exist. This assertion is supported by the finding that subsequent published studies have demonstrated that early tocilizumab administration showed an improvement in illness severity in critically ill COVID-19 patients, as defined by the requirement of ICU level of care [25]. It has also since been shown that tocilizumab fails to prevent progression to critical illness despite the mortality benefit [26].

In this study, while the presented data are weak, they do suggest that further investigation of baseline IL-6 levels as a marker of potential responsiveness to tocilizumab administration might further help to identify patients for whom a benefit from the intervention may be possible. Additionally, since an association between IL-6 levels and mortality following the administration of tocilizumab was not detected, this intervention may either represent detection of proinflammatory suppression or simply diminish the prognostic value of IL-6 measurement.

In addition, this study also shows that the established prognostic value of the inflammatory biomarkers CRP, LDH, and D dimer is likely diminished in the setting of tocilizumab administration, similar to findings of IL-6 associations.

There are significant limitations to this study, in particular the small sample size and the selection bias created by the inclusion of only those patients for whom the clinical decision to check IL-6 was deemed useful by the provider. This may suggest a sample with greater acuity, the potential for greater diagnostic uncertainty, or the presence of a confounding comorbid condition. Other weaknesses include lack of blinding or randomization, and the retrospective observational design. A strength, or, more precisely, point of interest for this study is that it reflects an on-the-ground analysis employed in a novel situation when information was scarce and uncertainty was high.

Though significant research into the benefits of tocilizumab has since been conducted and published, there remains an opportunity to further evaluate the use of IL-6 levels in guiding the clinical decision for, and timing of, tocilizumab administration and providing prognostic utility. Given the continued burden of COVID-19 and the evolving endemic nature of the disease, further investigation into IL-6 as a marker of disease severity and tocilizumab as an intervention, with attention to identification of a subset of patients in whom a more robust response may be expected, is warranted.

While the data presented here are limited, they support the body of literature guiding COVID-19 management and also serve as an example of a local evaluation in the early uncertain phases of the pandemic, and, as such, may be understood to yield certain useful concurrent insights.

5. Conclusions

In those with high levels of IL-6, an association of improved mortality with administration of tocilizumab was suggested, but no association was shown in those with low levels.

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Informed Consent Statement: Informed consent was waved due to the absence of identifiable data within the preexistent dataset and inability to identify subjects.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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