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Implications of tocilizumab based COVID-19 treatment on liver function tests: A one month retrospective analysis of unprecedented tocilizumab use during the peak of the SARS-CoV-2 pandemic in New York

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ABSTRACT

Aims: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with a spectrum of gastrointestinal (GI) symptoms and elevated liver-related tests (LRTs). It is unclear if GI pathology and liver injury are related to direct SARS-CoV-2 viral effects, drugs used for treatment, a systemic inflammatory response, or a complicated disease course. Our retrospective study aimed to assess the effects of tocilizumab (TCZ) on GI symptoms, LRTs, and coagulation factors in SARS-CoV-2 patients hospitalized during April 2020.

Methods: A retrospective chart review was conducted, evaluating for the prevalence of vomiting, diarrhea, changes in LRTs, and coagulation panels in all SARS-CoV-2 patients admitted during April 2020. The study group included 69 patients who received TCZ and the control group included 73 patients who did not receive TCZ.

Results: Liver function tests (LFTs) increased after TCZ administration when compared to LFTs in the control group. Study group versus control group: aspartate aminotransferase (AST) [75±49.18 vs 63±15.03 p<0.01 95% CI (confidence interval)], alanine aminotransferase (ALT) (71.73±57.4 vs 54±18.10 p<0.01 95% CI); alkaline phosphatase (ALP) (104.85±56.91 vs 74.46±8.92 p<0.01 95% CI). Total bilirubin (TB) showed no significant change (0.64±0.42 vs 1±0.31, p=0.4 95% CI). International normalized ratio (INR) showed an increase in the test group (1.27±0.01 vs 1±0.26, p<0.01 95% CI). Only 36% of patients had viral hepatitis studies prior to receiving TCZ. Although not statistically significant, 19% of patients reported vomiting and diarrhea prior to TCZ, 38% of whom reported symptom resolution after treatment. There was no significant improvement in sepsis management after the treatment (34 vs 35 p:0.06 95% CI).

Conclusion: In our study, TCZ use was associated with an increase in ALT, AST, and INR and a decrease in TB. It is difficult to assess whether this rise in ALT is due to SARS-CoV-2 or a consequence of TCZ itself.

Keywords: COVID-19, Liver, Liver function test, Pneumonia, SARS-CoV-2

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) surprised the world in 2020 with its high contagiousness, rapid global spread, and overwhelming burden on healthcare systems internationally. Challenged with an unprecedented disease and a death toll quickly reaching over 160,000 people in the United States and 32,000 in New York alone [1]. Physicians rapidly and widely adopted the use of medications, off-label, to combat the coronavirus disease (COVID-19), often implementing the use of these therapies based on promising yet small observational studies, with minimal guidance. In addition to a potentially fatal lung injury, COVID-19 is associated with a spectrum of gastrointestinal (GI) symptoms and elevated liver function tests (LFTs). It is unclear if GI pathology and liver injury are directly related to SARS-CoV-2 viral effects, an often-complicated disease course, a systemic inflammatory response, or the drugs used to treat COVID-19.

One of the medications that was widely adopted at the onset of the COVID-19 pandemic was tocilizumab (TCZ). Tocilizumab, a monoclonal humanized anti-interleukin-6 receptor antagonist, is indicated for rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, and severe or life-threatening chimeric antigen receptor (CAR) T cell-induced cytokine release syndrome (CRS) [1, 2]. With the early recognition that SARS-CoV-2 is associated with a strong upregulation of cytokine and interferon production in causing pneumonia, in conjunction with promising anecdotal evidence of TCZ use in treating COVID-19 patients in China, TCZ garnered a lot of attention as a potential treatment focused on quelling the uncontrolled systemic inflammatory response associated with SARS-CoV-2. This medication is categorized under investigational use by the United States Food and Drug Administration for the treatment of SARS-CoV-2, the efficacy of which thus far is unproven [3]. Given the early and wide clinical use of TCZ in combating SARS-CoV-2, as well as the association between COVID-19 and liver injury, it is important to assess the potential effect of TCZ on LFTs. Our study aims to evaluate the usefulness of TCZ in SARS-CoV-2 patients and its effects on GI symptoms, LFTs, coagulation panels, and sepsis.

MATERIALS AND METHODS

In this retrospective, single-center study at Nassau University Medical Center, a safety-net hospital in New York, a chart review was performed on 142 patients who were SARS-CoV-2 positive from April 1 2020 to April 30 2020. The study group included 69 (48%) of these patients who received TCZ and the remaining 73 patients who did not receive TCZ were in the control group. In order to have received TCZ the patient's inflammatory markers needed to be two times the upper limit of normal prior to administration. Age, sex, and comorbidities among both groups were matched and they were analyzed for mortality, length of stay, changes in LFTs, coagulation panels, and sepsis. The presence of GI symptoms (diarrhea and vomiting), interleukin-6 (IL-6) levels, LFTs, and coagulation panels prior to and after receiving TCZ were reviewed. Patient's inflammatory markers and LFTs were reviewed prior to administration and over a 10 day period after TCZ was given. The highest IL-6 levels were documented before and after drug administration. ALT and AST greater than 40 U/L were considered elevated, while ALP levels greater than 116 U/L were considered elevated. In addition, we investigated how many patients had hepatitis viral panels checked prior to receiving TCZ. Once the data collection was complete R software was used to perform statistical analysis using a T-test and Fisher test.

RESULTS

Liver function tests increased after TCZ administration when compared to LFTs in the control group. Study group versus control group: AST (75±49.18 vs 63±15.03 $p<0.01$ 95% CI), ALT (71.73±57.4 vs 54±18.10 $p<0.01$ 95% CI); ALP (104.85±56.91 vs 74.46±8.92 $p<0.01$ 95% CI). Total bilirubin (TB) showed no significant change (0.64±0.42 vs 1±0.31, $p=0.4$ 95% CI). INR showed an increase in the test group (1.27±0.01 vs 1±0.26, $p<0.01$ 95% CI). Only 36% of patients had viral hepatitis studies prior to receiving TCZ. Although not statistically significant, 19% of patients reported vomiting and diarrhea prior to TCZ, 38% of whom reported symptom resolution after treatment. There was no significant improvement in sepsis management after the treatment (34 vs 35, p:0.06 95% CI).

DISCUSSION

Faced with a novel disease of lethal and pandemic proportions, scientists and physicians began using tocilizumab in the hopes that inhibiting the IL-6 signal transduction pathway may be the key to reducing the systemic inflammatory response implicated as a cause of bilateral diffuse alveolar injury and subsequent mortality seen in severe cases of COVID-19 [4].

In our study, TCZ use was associated with an increase in ALT, AST, ALP, and INR and no significant change was noted in total bilirubin. As COVID-19 patients have been reported to have elevated LFTs and TCZ has been implicated in elevation of ALT levels in up to 6% of patients [1], it becomes challenging to assess whether this rise in LFTs is due to the disease process or a consequence of TCZ itself. This is an important consideration, as the elevated liver enzymes observed in our patients may be due to the yet unknown pathophysiology behind SARS-CoV-2 or medication induced or a combined effect.

The pathophysiology behind elevation of LFTs in viral diseases is not well understood, abnormal LFTs have been reported in other COVID-19 patients as well. For example, Ong et al. discussed a study conducted in Shanghai, which showed that out of 148 patients infected with SARS-CoV-2, 50% had abnormal LFTs. Elevation of LFTs has also been observed with a multitude of different viral infections, familiarly seen with viruses as common as influenza itself. Sellers et al. found that 97% of patients infected with AH1N1 had elevated ALT and AST. They also found elevated LFTs in 60% of patients infected with AH5N1 and in 66% of patients infected with AH7N9.

On the other hand, studies have also shown that an association between IL-6 inhibitors and elevated LFTs regardless of the disease being treated. A mini-review of TCZ conducted by Venkiteshwaran in 2009 stated that prior to this drug being FDA approved and released on the market, clinical trials showed that it affected lipid levels and LFTs [5]. It was hypothesized that this was a consequence of IL-6 targets being present on hepatocytes. The mechanism of tocilizumab-induced liver injury is not well understood. Elevation of ALT has been thought to be a consequence of TCZ's direct effect on the immune system in the setting of a low hepatic metabolism or by being involved in the IL-6 pathway in the process of liver regeneration [6]. However, liver injury with TCZ appeared to be dose and duration related. Although the patients' in our study have only received a one-time dose of TCZ, the elevation of LFTs may be associated more so with TCZ or a combined effect of the COVID-19 disease [6] and TCZ as its use was significantly associated with an increase in ALT, AST, ALP, and INR.

Furthermore, only 36% of patients had viral hepatitis studies prior to initiating therapy due to the emergent nature of COVID-19 treatment, an important consideration given possible hepatitis reactivation with monoclonal antibody use. Le-Feng Chen et al. conducted a study which suggested a higher risk of hepatitis B infection reactivation in rheumatoid arthritis patients who received at least three doses of TCZ [7]. Francesca De Nard et al. discussed how multiple fields are now concerned about immunosuppressive medications reactivating hepatitis B in patients with surface antigen carriers and in surface antigen negative patients [8]. This further suggested that it may be beneficial to assess viral hepatitis status and to treat with antivirals prior to using immunosuppressants. Thus, studies with hepatitis panels obtained on all patients before and after monoclonal antibody administration would be beneficial to investigate the effect of monoclonal antibodies on reactivation and the need for antiviral agent co-administration.

According to our study results, the use of tocilizumab in COVID-19 patients showed no improvement in mortality as compared to the test group (17 vs 13, p=0.7 95% CI). Tocilizumab was not significantly beneficial in improving LFTs. According to our study results using TCZ in COVID-19 patients showed no significant benefit in relation to mortality and length of stay. However, our study population had a small sample size; hence, the CI was wide. Campochiaro et al. conducted a study in Milan, Italy on 65 patients. Their standard protocol therapy included administration of hydroxychloroquine, lopinavir/ritonavir, ceftriaxone, and azithromycin. Out of 65, 32 received TCZ along with standard medical therapy. On the other hand, 33 received standard therapy only. Similar to our study the majority of their patients were male. Their study did not observe a significant benefit in treating COVID-19 with TCZ either.

Given the lack of understanding of COVID-19 disease, management in early 2020 and New York being the first state to get destroyed with this disease, post-treatment follow-up has been limited as many patients expired despite medical treatment at the time or avoided in hospital follow-up. We need future studies with a higher sample size for better prediction of the drug efficacy and its side effects while treating COVID-19. To date, our experience with tocilizumab in SARS-CoV-2 is still limited as there is no standardized treatment plan.

CONCLUSION

Tocilizumab did not appear to have a significant beneficial impact on LFTs in COVID-19. It is still unclear as to whether the elevation ALT/AST, and INR are related to the disease process itself or a side effect of TCZ or both. As prior studies have suggested that the duration of monoclonal antibody use appears to be associated with elevation of LFTs in other diseases, we are leaning toward the idea that the elevation in LFTs in COVID-19 patients is due to the disease process itself. Additionally, it is prudent to check viral hepatitis status prior to initiating therapy and this was not at the forefront of the mind among practitioners within this study population in light of the urgency of treatment that this pandemic demanded of us. Further evaluation with a larger sample size is warranted to continue to assess the potential implications of TCZ use.

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Author Contributions

Kristen Farraj – Conception of the work, Design of the work, Acquisition of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Saher Sheikh – Conception of the work, Design of the work, Acquisition of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ross Imbrie – Design of the work, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Rajmohan Rammohan – Analysis of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Guarantor of Submission

The corresponding author is the guarantor of submission.

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Consent Statement

Consent was unable to be obtained as it is a retrospective study conducted during a pandemic and most of the patients in this study unfortunately expired. IRB approval was obtained and an exception was given in regard to consent due to the situation at the time.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.