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Title:

Letter to the Editor: Acute hypertriglyceridemia in patients with COVID-19 receiving tocilizumab

Running Title: Acute hypertriglyceridemia in COVID-19 treated with tocilizumab

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Abstract

Tocilizumab is an interleukin-6 (IL-6) receptor antibody and is progressing as a viable and promising treatment option in patients with severe coronavirus disease 2019 (COVID-19). IL-6 is known to have both immunomodulatory and metabolic actions. In this letter we outline two cases of acute hypertriglyceridemia in patients with COVID-19 treated with tocilizumab: one with elevated biomarkers consistent with acute pancreatitis the other without. Given the paucity of robust clinical trial data for most COVID-19 pharmacotherapies at this time, clinicians should continue to remain steadfast in recognition of interventions that improve clinical outcomes and vigilant in monitoring for acute adverse effects that are difficult to detect in clinical trials with small sample sizes. The observations from our two cases highlight the complex, not fully elucidated interrelationship between elevated IL-6 and pharmacologic interventions impacting this pathway. Clinicians should consider monitoring for hypertriglyceridemia and acute

pancreatitis as described with chronic tocilizumab use for rheumatoid arthritis in those receiving it for COVID-19.

Keywords

Coronavirus < Virus classification, Interleukin < Immune responses, Immunodulators < Disease control

Dear Editor:

We applaud Luo et al. for describing their experience with tocilizumab as a treatment option for severe coronavirus disease 2019 (COVID-19).[1] Patients with COVID-19 have been reported to have elevated IL-6 levels.[1,2] Tocilizumab (TCZ), an interleukin-6 (IL-6) receptor antibody, has emerged as a viable treatment option in severe COVID-19 with no acute adverse events described to date.[1,2] These safety observations coincide with literature assessing short courses of TCZ in patients receiving chimeric antigen receptor T-cell therapy that develop cytokine release syndrome (CRS).[3] Chronic use of TCZ in rheumatoid arthritis (RA) has been shown to increase lipid parameters, in particular triglycerides.[4] Furthermore, acute pancreatitis (AP) has been associated with chronic TCZ treatment of RA with development of AP described as early as two weeks after initiating therapy.[5] Literature for acute indications of TCZ does not report triglycerides or parameters for AP.[2,3] Thus, little is known about the short-term adverse effects and what parameters should be monitored in those with COVID-19 receiving TCZ. We have used TCZ in patients with severe COVID-19 with elevated inflammatory markers (IL-6, lactate dehydrogenase, d-dimer, ferritin), and severe acute respiratory distress syndrome (ARDS) with no alternative diagnosis. Here, we outline two cases of acute hypertriglyceridemia in patients with COVID-19 treated with TCZ (Figure 1), one with elevated inflammatory biomarkers consistent with AP the other without.

Case 1 was a 65 year old male admitted to the intensive care unit (ICU) with respiratory failure and ARDS eight days after symptom onset. At that time, he received lopinavir/ritonavir, ribavirin, and hydroxychloroquine. Sedation was provided with a propofol infusion. Tocilizumab was administered on day 9 and 10 due to persistent fevers, severe ARDS, and elevated

inflammatory markers. Propofol was discontinued on day 10 prior to the second dose of tocilizumab. On day 11, serum TG levels (1196 mg/dL) and AP biomarkers (Amylase:309 IU/L, Lipase: 104 IU/L) were significantly increased. Case 2 was a 43 year old male admitted to the ICU with respiratory failure and ARDS twelve days after symptom onset and was also treated with lopinavir/ritonavir, ribavirin, and hydroxychloroquine. Sedation was provided with propofol. TCZ was initiated on day 13 for persistent fevers, severe ARDS, and elevated inflammatory markers. Propofol was changed to midazolam on day 13, six hour before initiating TCZ. After tocilizumab administration, serum TG levels peaked on day 16 (1436 mg/dL) and AP biomarkers remained normal (Amylase: 47 IU/L, Lipase: 58 IU/L). In both cases HLH was lower on the differential using the HLH-2004 diagnostic criteria and HLH-probability calculator, enteral feeding had not been initiated, and early rapid increases of TG was felt to be uncharacteristic of short courses of propofol (case 1: 54 hours with dose ranging from 5-60 mcg/kg/min, case 2: 28 hours with dose ranging from 5-55 mcg/kg/min). The Naranjo probability scale assigned a probable (score: 7) relationship between TCZ and hypertriglyceridemia for both cases. Due to safety concerns in the transporting of critically ill patients and infection control implications of patients with COVID-19, imaging was not conducted in either case to asses for AP.

These cases highlight several important monitoring parameter, pharmacotherapy, and diagnostic considerations regarding the care of critically ill patients with COVID-19 receiving TCZ. IL-6 has both immunomodulatory and metabolic actions. Acute IL-6 elevations mobilize free fatty acid via adipocytes.[7] IL-6 stimulates skeletal muscle uptake of glucose and free fatty acid from the serum.[6] The exact mechanism by which chronic TCZ use contributes to TG elevations remains to be elucidated.[4] Membrane-bound and soluble IL-6 receptor inhibition by acute TCZ administration may result in increased TG levels by interfering with these metabolic pathways. While propofol is known to increase TGs secondary to the lipid emulsion vehicle, this effect is typically seen 2.25-7 days after initiating therapy with normalization occurring within 72 hours.[7-9] This population may be more prone to hypertriglyceridemia development with propofol use given the metabolic activities of IL-6 and may warrant more frequent monitoring.

TCZ is progressing as a viable and promising treatment option in patients with severe COVID-19. Given the paucity of robust clinical trial data for most COVID-19 pharmacotherapies at this time, clinicians should continue to remain steadfast in recognition of interventions that improve clinical outcomes and vigilant in monitoring for acute adverse effects that are difficult to detect in clinical trials with small sample sizes.[10] The observations from our two cases highlight the complex, not fully elucidated interrelationship between elevated IL-6 and pharmacologic interventions impacting this pathway. Clinicians should consider monitoring for hypertriglyceridemia described with chronic TCZ use in patients with COVID-19 treated with TCZ.

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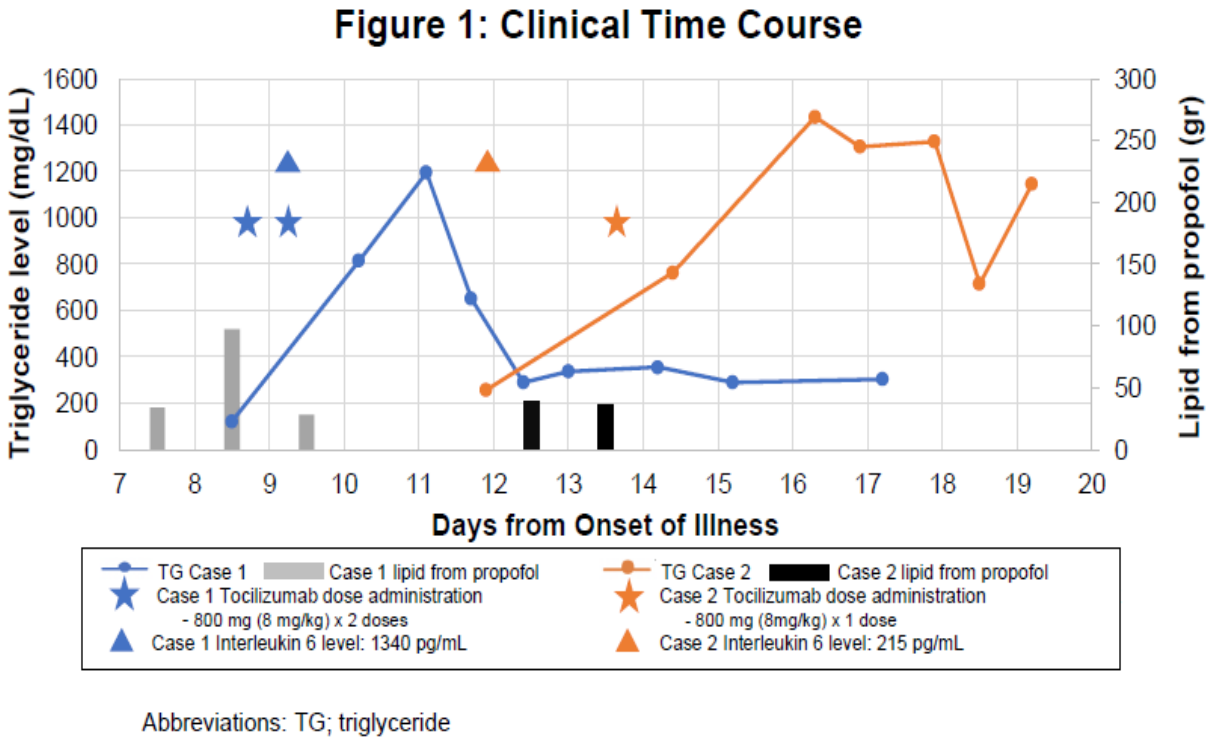
Figure



Abbreviations: TG; triglyceride