



SEVERE HYPERTRIGLYCERIDEMIA DUE TO TOCILIZUMAB IN COVID-19 TREATMENT: A CASE REPORT

Hipertrigliceridemia grave por tocilizumabe no tratamento da covid-19: relato de caso

Wictor Hugo Oliveira Leles^{1*}, Álique Franco Pinheiro Alves Capop¹ , Aline de Brito Soyer² 

RESUMO

Introdução e objetivo: a doença do coronavírus 2019 (COVID-19), causada pelo SARS-CoV-2, tem sido extensivamente estudada nos últimos anos. O tocilizumabe, um anticorpo monoclonal anti-receptor de interleucina-6, foi recentemente usado para o tratamento de inflamação crônica grave em pacientes com COVID-19. No entanto, há escassez de informações sobre os efeitos colaterais associados ao uso de tocilizumabe em pacientes com COVID-19. Assim, nosso objetivo é apresentar o caso de um paciente com complicações após infecção por COVID-19 que recebeu tratamento com tocilizumabe. **Descrição do caso:** paciente jovem, caucasiano, do sexo masculino, com hipertrigliceridemia grave, pancreatite aguda e diabetes mellitus após tratamento com tocilizumabe para COVID-19. Este estudo foi descritivo e observacional, e seus dados foram coletados por meio de anamnese detalhada e avaliação de exames laboratoriais e de imagem realizados após infecção por COVID-19 e internação para tratamento de pancreatite aguda. **Conclusão:** Este caso é um lembrete de que uma compreensão mais ampla deste medicamento é fundamental para que os profissionais de saúde possam identificar e tratar seus efeitos colaterais o mais cedo possível.

Palavras-chave: Hipertrigliceridemia, COVID-19, Pancreatite Aguda, Diabetes Mellitus.

ABSTRACT

Introduction and aim: Coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, has been extensively studied in recent years. Tocilizumab, an anti-interleukin-6 receptor monoclonal antibody, is recently used for the treatment of severe chronic inflammation in patients with COVID-19. However, there is a paucity of information on the side effects associated with the use of tocilizumab in patients with COVID-19. Thus, we aim is to present a case of a patient with complications after COVID-19 infection who received treatment with tocilizumab. **Case description:** We present the case of a young, Caucasian, male patient with severe hypertriglyceridemia, acute pancreatitis, and diabetes mellitus after tocilizumab treatment for COVID-19. This study was descriptive and observational, and its data were collected through detailed anamnesis and evaluation of laboratory and imaging tests performed after COVID-19 infection and hospitalization for the treatment of acute pancreatitis. **Conclusion:** This case is a reminder that a broader understanding of this drug is imperative for healthcare providers to be able to identify and treat its side effects as early as possible.

Keywords: Hypertriglyceridemia, COVID-19, Acute Pancreatitis, Diabetes Mellitus.

1. Acadêmico do curso de Medicina da Faculdade Morgana Potrich (FAMP), Mineiros-GO, Brasil.

2. Médica Endocrinologista, Docente no curso de Medicina da Faculdade Morgana Potrich (FAMP), Mineiros-GO, Brasil.

*Autor para Correspondência: wictor_oliveira@hotmail.com



INTRODUCTION

Tocilizumab (TCZ) is a humanized monoclonal antibody that prevents the binding of IL-6 with its receptor and is used mainly for the treatment of rheumatoid arthritis (6,7). TCZ is indicated as a treatment option for severe cases of coronavirus disease 2019 (COVID-19) because of the high levels of interleukin-6 (IL-6) observed in these patients (1-5). High levels of IL-6 stimulate chronic inflammation, by inducing a cytokine storm, and worsen clinical symptoms and treatment outcomes in patients with COVID-19 (6). TCZ can help in the treatment of patients with severe COVID-19 by inhibiting IL-6 and modulating their inflammatory process (1,2,8,9).

The use of TCZ is associated with changes in the lipid profile, particularly elevated serum triglyceride levels in patients with COVID-19 (10,11). Hypertriglyceridemia is the third most common cause of acute pancreatitis (AP) and is observed in 10–20% of individuals with serum triglyceride levels above 2000 mg/dL (12).

Hyperlipidemia-induced pancreatitis can cause diabetes in 86% of cases (13), raising public health concerns in Brazil. It is worth noting that, aside from pancreatic disease or diabetes of the exocrine pancreas, diabetes mellitus as a result of other etiological factors is rarely considered in daily practice (14,15).

The objective of this study was to report the case of a young patient with severe hypertriglyceridemia, who developed acute pancreatitis and diabetes mellitus two weeks after treatment with tocilizumab for COVID-19. This case serves as a warning and draws the attention of healthcare providers to the serious adverse effects of tocilizumab.

The reported data were obtained from a detailed anamnesis, analysis of laboratory and imaging tests, and data collection from electronic medical records in a retrospective and descriptive manner. The information described is only scientifically and clinically relevant for the understanding of the case.

The study was reviewed and approved by the Research Ethics Committee of Faculdades Integradas de Santa Fé do Sul (number 5,271,165) on March 3, 2022. CAAE: 53646221.6.0000.5428.

CASE DESCRIPTION

In May 2021, a 35-year-old, 81kg, height of 184 cm, body mass index (BMI) of 23,9, Caucasian, male patient, with a confirmed diagnosis of COVID-19, was referred to our hospital on the 12th day after the onset of symptoms. The patient presented with symptoms such asodynophagia, cough, and fever. He developed dyspnea and had a decreased oxygen saturation (SpO₂, 85%). He was immediately placed

on noninvasive ventilation, and treatment with corticosteroids, intravenous (IV) tocilizumab in a continuous infusion pump, ceftriaxone, and Clexane was initiated.

He reported a remission of symptoms and was released from the hospital seven days after his admission. However, after two weeks, he began to experience severe abdominal pain, nausea, and vomiting and was admitted again. Laboratory tests revealed the following: triglyceride, 7,680 mg/dL; total cholesterol, 904 mg/dL with markedly high lipemic serum; fasting glucose, 498 mg/dL; and glycated hemoglobin (HbA1C), 12.3%. Abdominal computed tomography confirmed acute pancreatitis. Supportive treatment for acute pancreatitis, in addition to rosuvastatin (20 mg), ciprofibrate (100 mg), and subcutaneous rapid-acting insulin plus insulin glargine was initiated.

He reported a history of systemic arterial hypertension, pre-diabetes, and mild mixed dyslipidemia, without the need for drug treatment. He had no prior history of alcoholism or smoking. However, he had a family history of hypertension; his father and mother died at age of 66 and 61, respectively, due to COVID-19 complications.

After seven days of treatment, the patient developed a significant reduction in glycemic levels, triglycerides (637 mg/dL), and total cholesterol (396 mg/dL). He was discharged from the hospital and was prescribed insulin glargine 22 IU, Rosuvastatin 20 mg, Ciprofibrate 100 mg, and Losartan 100 mg/day.

He was examined again in July 2021. His laboratory test results were normal, and he presented no complaints. The capillary blood glucose level of the patient was between 54 to 133 mg/dL, and he had an HbA1C of 6.4%. Thus, the insulin glargine dose was gradually reduced and finally discontinued in early August 2021.

Currently, the patient is on a low-carbohydrate diet and takes only ciprofibrate (100 mg) and rosuvastatin (20 mg) and has no complaints.

DISCUSSION

The mechanism of action of TCZ in the treatment of COVID-19 remains to be elucidated. Previous studies have shown that IL-6 is found in small amounts in fibroblasts, endothelial cells, and tumor cells, in addition to immune cells, such as B lymphocytes, T lymphocytes, macrophages, and monocytes (16).

The recommended dose of TCZ is 4-8 mg/kg or 400 mg IV and can be repeated every 12 hours and must not exceed 800 mg per day. However, there is a lack of data on the disease stage in which Tocilizumab must be administered.

Moreover, IL-6 has not yet been established as a biomarker of disease progression or severity of COVID-19 (5,7,17,18).

Currently, TCZ is only used in critically ill patients receiving steroids, showing signs of inflammation, and having increased oxygen requirements. Its application in other clinical situations has proven to be more harmful than beneficial (19).

According to Flaig et al (2016), that increase in triglycerides occurs suddenly, usually around two weeks after drug use, similar to the case reported (20).

No preprints on the efficacy or safety of tocilizumab in the context of COVID-19 have been published or made available to date, despite studies demonstrating more favorable treatment outcomes with tocilizumab use compared to standard care in patients with severe or critical COVID-19 (6).

Although randomized controlled trials have shown that TCZ does not reduce short-term mortality, cohort studies suggest an association between TCZ and lower mortality. Moreover, there is still evidence that TCZ reduces the risk of mechanical ventilation in patients hospitalized with COVID-19 (21).

A combination of physical activity, a low-carbohydrate and low-fat diet, and drug therapy is recommended for cases with severe hypertriglyceridemia (>1000 mg/dL). Fibrates are the preferred first-line drugs to lower triglycerides in patients at risk for triglyceride-induced pancreatitis. Three classes of drugs (fibrates, niacin, and omega-3 fatty acids) alone or in combination with statins are suggested as treatment options in patients with moderate to severe triglyceride levels (12,22). As a result, the patient in this study was treated with rosuvastatin and ciprofibrate; in addition, lifestyle changes were also implemented.

Li et al (2021) explained that overactivated inflammatory responses in people infected with SARS-CoV-2 can contribute to insulin resistance and high blood glucose, and this could explain the worsening of the patient's hyperglycemic condition in our study (24).

Insulin exerts anti-inflammatory effects in humans and reduces inflammatory biomarkers in individuals hospitalized with severe disease. Insulin has been widely used in cases of bacterial or viral infections complicated by diabetes. Most hospitalized patients with COVID-19, especially those with respiratory distress, should be given insulin to maintain glycemic levels (23).

Several studies have suggested that the use of insulin is effective in reducing triglyceride levels and the risk of acute pancreatitis (10). In the aforementioned case, the use of insulin proved advantageous in reducing triglyceride levels and controlling glycemic levels.

Therefore, the case presented here is characterized by diabetes due to pancreatitis, as the patient had high glycemic levels only after the AP episode, aside from the fact that COVID-19 had a role in triggering diabetes.

Tocilizumab is well known to cause hypertriglyceridemia, but here we report a patient with COVID-19 treated with TCZ who developed acute hypertriglyceridemia at levels much higher than those reported in the literature (7,680 mg/dL).

It can be seen that TCZ, in association with corticosteroids, has been used in patients with severe COVID-19 and exacerbated chronic inflammation. However, it has potential adverse effects, such as hypertriglyceridemia, acute pancreatitis, diabetes mellitus, and higher mortality. Thus, tocilizumab should be carefully considered before clinical use.

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