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TOCILIZUMAB IN COVID-19 SEVERE CASES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: COVID-19 is a medical emergency that has affected the world's population. Severe cases of COVID-19 have been treated with Tocilizumab, a monoclonal antibody that inhibits interleukin-6 (IL-6), to prevent a possible cytokine storm. However, there is insufficient data to prove its effectiveness and impact in reducing mortality rate. Therefore, we have developed a systemic review to compare the efficacy in treating COVID-19 severe cases between Tocilizumab group of patients and standard care group of patients.

Methods: We performed a literature research using "tocilizumab" or "COVID-19" or "COVID-19 severe cases" using Nature, PubMed, The Lancet, Science Direct, QJM-Oxford Academic. The online databases used in the study were from March 2020 to February 2021.

Results: Two studies, one case control study (n = 193 patients) and one single center cohort study (n = 132 patients) were selected in the study. Mortality rate (MR) for patients who received Tocilizumab treatment (n =132, 49,84%; MR =37,65%) was significant lower than MR for patients who received standard care (n = 163, 50,15%; MR = 44,78 %).

Key words: Tocilizumab, COVID-19, Mortality, Severe Cases, SARS-COV2

INTRODUCTION

In December 2019, a new coronavirus called "severe acute respiratory distress syndrome coronavirus 2" (SARS-CoV-2)[1] appeared in Wuhan, the capital of Hubei in China. On 30 January 2020, a public health emergency of international interest was declared[2]. Due to its contagiousness, the virus has reached pandemic levels, affecting 221 countries, causing over 114 million infections and over 2 million deaths until March 2021[3]. In the United States, the number of patients with COVID-19 is the highest, followed by India, Brazil, Russia and the United Kingdom. In China, the number of confirmed cases has reached 89,912[4]. It is generally believed that the incubation period is two weeks, but there is no unified conclusion yet. It is the third most contagious coronavirus, followed by severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012[5], which represents a medical and public challenge. SARS-CoV-2 showed similar infection patterns and clinical features, but compared to the two previous coronavirus outbreaks[6], the transmission rate was even faster[7]. However, a special feature is that patients infected with SARS-CoV and MERS-CoV and patients with COVID-19 have all developed systemic inflammatory response syndrome and acute respiratory distress syndrome (ARDS)[8].

Cytokines and the cytokine storm are a key risk factor in the severity of COVID-19. An increase in interleukin-6 levels has been correlated with the severity and even mortality in severe cases of COVID-19. Interleukin-6 (IL-6) is a multifunctional cytokine, which acts on B and T cells, hematopoietic stem cells, hepatocytes and neurons. In the process of acute inflammation related to injuries, trauma and brain damage, the production of IL-6 is induced rapidly. Therefore, many COVID-19 severe patients were administered Tocilizumab, an interleukin-6 (IL-6) inhibitory monoclonal antibody, in order to reduce inflammation and prevent a possible cytokine storm.

MATERIALS AND METHODS

The data collection was performed by two researchers using "tocilizumab" or "COVID-19" or

„COVID-19 severe cases" on online platforms like Nature, PubMed, The Lancet, Science Direct, QJM-Oxford Academic. The online databases used in the study were from March 2020 to February 2021.

Initially, eight studies were included in the research, one single center cohort study (1), one case control study (1), two retrospective cohort studies (2), two randomized controlled trial (2), one single center study (1) and one meta-analysis systematic review (1), with a total of 2223 patients. Articles in the form of review, abstract only, randomized controlled trial and articles that did not include a comparison of mortality rates between patients who received standard care and patients who received Tocilizumab, were excluded.

EXPERIMENTAL PART

Two articles were included in the study, one case control study conducted in New York, USA, with a total of 193 patients[9] (*n* = 193 patients) and one single center cohort study with a total of 132 patients[10] (*n* = 132 patients). A total of 325 patients were included in the study, divided by two categories: patients with severe COVID-19 who received standard care (*n* = 163 patients) and patients with severe COVID-19 who received Tocilizumab (*n* =162 patients).

The main parameter followed in the two articles studied was the mortality rate. We compared the mortality rate between patients with severe COVID-19 who received tocilizumab and patients with severe COVID-19 who were treated with the standard protocol. Patients' demographic and clinical characteristics were also taken into account.

RESULTS AND DISCUSSION

In this meta-analysis including 325 patients divided by two main categories, patients with severe COVID-19 who received standard care (*n* = 163 patients) and patients with severe COVID-19 who received Tocilizumab (*n* =162 patients), the mortality rate (MR) for patients who received Tocilizumab treatment (*n* =132, 49,84%; MR =37,65%) was significant lower than MR for patients who received standard care (*n* = 163, 50,15%; MR = 44,78 %). The mean age was above 60 years and most patients were men (*n* = 233, 71,69%), 120 (*n* = 120, 74,04%) included in the Tocilizumab group and 113 (*n* = 113, 69,32 %) in the Standard care group. The analysis showed that the most common comorbidity among patients was hypertension (*n* = 176, 54,15%), both Tocilizumab and Standard care categories including a number of 88 hypertensive patients each (*n* = 88, 53,98%). Hypertension was followed by diabetes, 108 patients (*n* = 108, *33*,23%) were diagnosed with diabetes, 51 (*n* = 51, 31,48%) patients included in the Tocilizumab group and 57 (*n* = 57, 34, 96%) patients in the Standard care group. Laboratory values, including markers of inflammation such as ferritin and C-reactive protein (CRP), were found to be elevated in almost all patients. The mean ferritin for the Tocilizumab group of patients was 1289 (Ng/mL) and 1126 (Ng/mL) for the standard care group of patients, while the mean CRP was 14,36 (mg/dl) for the Tocilizumab group of patients and 13,21 (mg/dl) for the Standard care group of patients.

For COVID-19 severe cases management, most patients in both groups received azithromycin (79,01% in the Tocilizumab group and 82,20% in the standard care group) and hydroxychloroquine (91,97% in the Tocilizumab group and 93,86% in the standard care group). Other medication for COVID-19 management was also given, including corticosteroids (32,71% in the Tocilizumab group and 22,69% in the standard care group).

In terms of mortality rate, our main point of interest, a significant decrease was observed among Tocilizumab group of patients (37,65%) vs. Standard care group of patients (44,78%).

CONCLUSIONS

In conclusion, inflammation is an important part of the function of the immune system. SARS-CoV-2 may induce an excessive and prolonged cytokine response, leading to lung damage and multiple organ failure. This systematic review and meta-analysis summarize that using Tocilizumab for the management of COVID-19 severe cases, might decrease the rate of mortality.

The high spread of SARS-CoV-2 has forced all medical institutions around the world to conduct research, therefore new treatments are being developed. However, there is no specific antiviral treatment for COVID-19 severe cases. Hence the use of therapies that inhibit the production of proinflammatory cytokines may help reduce adverse inflammatory responses and increase survival rate.

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