Case Report

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Tocilizumabe Associated with Remdesivir on Severe Acute Respiratory Syndrome by Covid-19: Case Report on a Private Hospital in Salvador- Ba, Brazil

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ABSTRACT

The disease caused by SARS-CoV-2 demonstrated high morbimortality rate capability, with a higher lethality to some risk groups. The present article describes a case report from a male patient, 77 years old, vaccinated for more than two months with both doses of inactivated covid-19 vaccine, admitted to the emergency room with a history of, for over 5 days, flu-like symptoms with evolution, 3 days ago, with fatigue, tiredness, inappetence, cough, fever, and oxygen desaturation at home. Tested positive for Covid-19 through RT-PCR test. After evolution with deterioration of the respiratory function, the opportune introduction of Remdesivir and Tocilizumab on the therapeutic plan was associated with clinical and radiological improvement of the patient, avoiding invasive approaches of respiratory support and, therefore, reducing fatality risks.

KEYWORDS: COVID-19; SARS-CoV-2; Remdesivir; Tocilizumab

ABBREVIATIONS: NIV: Noninvasive Ventilation; MV: Mechanical Ventilation; HFNC: High Flow Nasal Catheter; COVID-19: Corona Virus Disease 2019; NRM: Non-Reinhalant Mask; BP: Blood pressure; HR: Heart Rate; RR: Respiratory Rate; BPM: breaths per minute; T: Body Temperature; Fi O2: Inspiratory fraction of O2; NC: O2 Nasal Catheter; PCR: Protein-C- Reactive; SatO2: O2 saturation in the blood; O2: Oxygen; CT: Computed Tomography

INTRODUCTION

The disease brought forth by the SARS-CoV-2 virus, designated COVID-19, appeared in December 2019, in the city of Wuhan, China. Later, in March 2020, the World Health Organization (WHO) declared a COVID-19 pandemic [1]. This disease was an acute respiratory infection with a high spreading rate and potentially severe, with a lethality rate of about 2% in Brazil [2].

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Usually, the clinical course of the disease is self-limited, characterized by a flu-like syndrome associated with systemic symptoms [3]. However, certain risk groups, such as elderly people and immunosuppressed patients can develop various pulmonary and systemic complications, possibly with the need for invasive respiratory support. This unfavorable evolution of COVID-19 can occur even in those individuals with a completed vaccinal scheme, given the variability of the vaccination efficacy [4]. This way, the rational use of pharmaceuticals in the hospital treatment of COVID-19, besides usual support measures, has shown to be essential for the reduction of the morbimortality rate and pandemic control, with a spotlight on the antivirals (i.e. Remdesivir) and the immunomodulators (i.e. Tocilizumab) [5].

Tocilizumab is an IL-6 receptor antagonist, a cytokine responsible for the increased inflammatory response to the SARS-CoV-2 infection. Its off-label use was considered for patients hospitalized with COVID-19 in the use of NIV or HFNC, especially with recent clinical deterioration and risk of progression to MV [6]. Clinical studies demonstrated that, in this context, medication reduced the death risk in 28 days, as well as time spent in the hospital and the risk of MV [7]. Meanwhile, Remdesivir is an antiviral that works by inhibiting the RNA-dependent polymerase of SARS-CoV-2, an enzyme essential for viral replication. Its use was considered primarily on patients with COVID-19 and the need for hospitalization or high risk of unfavorable progression [8]. Upfronted with the persistency of the pandemic of COVID-19 and the high relevancy of its socioeconomic repercussions, the effective use of pharmaceuticals became essential to reduce the hospitalization time, the need for invasive mechanical ventilation, and the morbimortality rate of patients with this disease. It describes and discussed the case of a 77-year-old patient that evolved with severity after infection by SARS-CoV-2. In this context, the combination of tocilizumab and remdesivir was used with favorable results.

CASE PRESENTATION

A 77-year-old male patient living in Salvador, Bahia, dyslipidemic using simvastatin, allergic to metoclopramide, and with a previous history of prostate and bladder neoplasia, received the second dose of SARS-CoV-2 vaccine on 09/04/2021. He was admitted on 06/12/2021 to the emergency department of a reference hospital in the city of Salvador-BA with a history of mild flu for 5 days, evolving for 3 days with fatigue, inappetence, sporadic cough, fever, and episodes 91-92% of O2 saturation measured in his residence, without complaint of dyspnea at the time. On initial physical examination, he was in good general condition, eupneic, afebrile, and with the following vital data: BP 146 x 72 mmHg; HR 89 bpm; T 35.8 °C; RR 18 bpm; SatO2 96%; without alteration to respiratory and cardiovascular examinations. On the date of admission, rt-PCR was performed for COVID-19, with a positive result. Leukocytes 6,430/mm^3 were identified on the blood count; Rods 0%; Segmented 86%; Eosinophils 2%; Lymphocytes 8%; Monocytes 4%; Atypical lymphocytes 0%; Hemoglobin 13.2 g/dL; Hematocrit 40%; and Platelets 187,000/mm^3. In addition, PCR 20.5 mg/dL; Urea 45 mg/dL; Creatinine 1.0 mg/dL; AST 39 U/L; and ALT 21 U/L. He was submitted to chest CT (Figure 1) that showed multiple pulmonary ground glass opacities, sometimes associated with interlobular septal thickening and thin reticular permeate, in addition to sparse foci of consolidation with bilateral multifocal distribution and peripheral and posterior predominance. These findings were consistent with COVID-19 viral pneumonia, with an estimated extension of around 25% of the pulmonary area. Treatment was started with Azithromycin 500 mg/day for 5 days; Pantoprazole 40 mg/day; Clexane 40 mg/day and Methylprednisolone 120 mg/day. On 13/06/2021, 36h after admission, the patient evolved with a drop in oxygen saturation, leading him to start 3 L/min of O2 with a good response. Later, clonazepam presented 0.5 mg. It responded with great drowsiness, tachypnea (26 bpm), and a drop in O2 saturation (87%), requiring an increase in the supply of O2 (5 L/min). There were no signs of respiratory effort, but he was transferred to the semi- intensive care unit. On the next day (14/06/2021), he was in bed in decubitus, lucid and oriented, eupneic, afebrile, sleepy, HR 76 bpm, BP 100 x 70 mmHg, with crackles in pulmonary bases and without other alterations on physical examination. It saturated between 94 and 97% with 3 L/min of O2 on spontaneous ventilation and with no signs of increased respiratory work but reported perception of weight in the chest. A second chest CT (Figure 2,3) was performed, which showed an increase in the extent of frosted glass opacities, associated with the thickening of interlobular septa and thin reticular pattern, presenting diffuse bilateral multifocal distribution; as well as the emergence of new areas of parenchymal condensation in the periphery of the apicoposterior segment to the right and in the posterior and subpleural region of the right lower lobe. The extent of pulmonary involvement was estimated at around 50%. Later, on the same date, the patient presented a sudden episode of o2 saturation drop to 60% with dyspnea, fever (38.4 °C) and chills, returning to 94-98% of SatO2 after the use of 15 L of O2 in NRM. There was no hypotension or lowering of the level of consciousness. On this date, ceftriaxone was associated with 1 g/day for 7 days; and Tocilizumab 600 mg (1st dose). The next day (15/06/2021), the patient presented SatO2 92-96% in MNR, HR 62 bpm, BP 134 x 67 mmHg, and crackles in pulmonary bases.

At night, it evolved with the need for CNAF 40 L/min and FiO2 100%, maintaining SatO2 94%. As of 06/16/2021, the patient was lucid, oriented, and hemodynamically stable, with SatO2 91-97% using CNAF (FiO2 90-100%). Due to the persistence of severe respiratory condition, Tocilizumab 200mg (2nd dose) treatment was added to the treatment; and Remdesivir 200mg (1st dose) and 100 mg/day for 5 days. The patient evolved on 17/06/2021 with good saturation using NIV (85% O2), interspersed with HFNC (90-100% O2). Between 18/06 and 28/06/2021, the patient was hemodynamically stable, but still borderline in the respiratory condition, keeping SatO2 88- 97% in alternating use of NIV and HFNC. It evolved between 29/06 and 08/07/2021 with progressive improvement from the clinical and laboratory point of view, using NC O2 1-3 L/min. He was discharged from the hospital on 07/09/2021 and was referred for rehabilitation with physiotherapy and support due to post-covid syndrome.

DISCUSSION

The clinical case described an elderly patient that was admitted to the Emergency Department with flu-like symptoms and a recent oxygen desaturation event. In the mind of the epidemiological context of the SARS-CoV-2 pandemic, the suspicion of COVID-19 was quickly confirmed through the RT-PCR exam. The case was classified as severe due to the appearance of low O2 saturation episodes, tachypnea, crackles in pulmonary bases, and, especially, due to the result of the chest CT, which demonstrated SARS-CoV-2 pneumonia. Besides the treatment of respiratory support, the introduction of Tocilizumab and the later combination with Remdesivir was associated with a gradual clinical improvement of the patient, which correlates with the progressive reduction of the amount of respiratory support needed to maintain an adequate SatO2. This way, the patient had a resolution of the pneumonic case and avoided an evolution with the need for invasive ventilation.

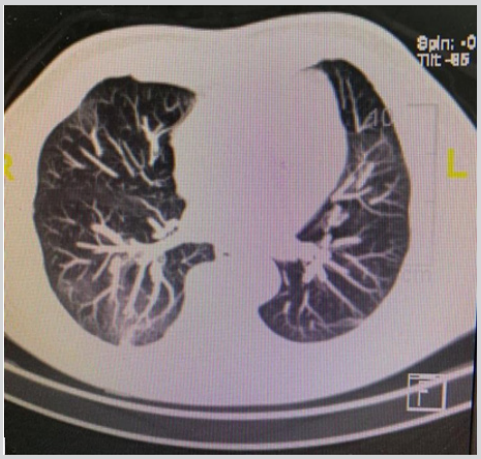

Figure 1: Patient imaging. Ct scan in transverse section.

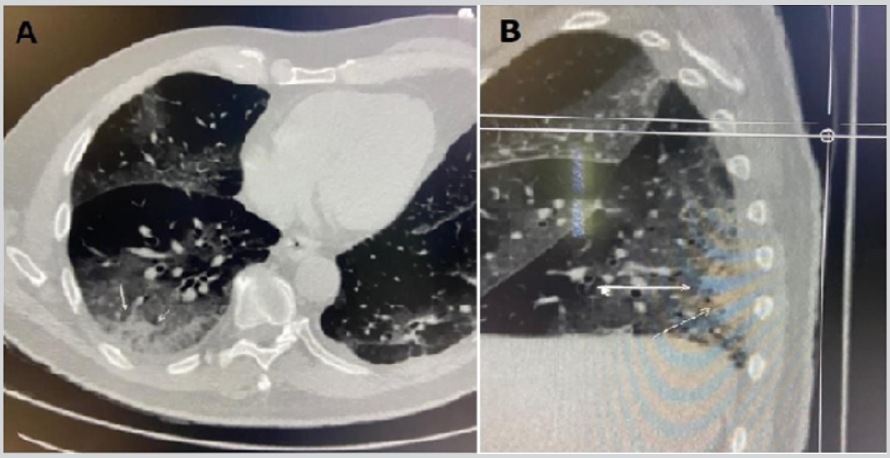

Figure 2: Patient imaging. (A) Cross-sectional chest CT. (B) chest CT in sagittal section.

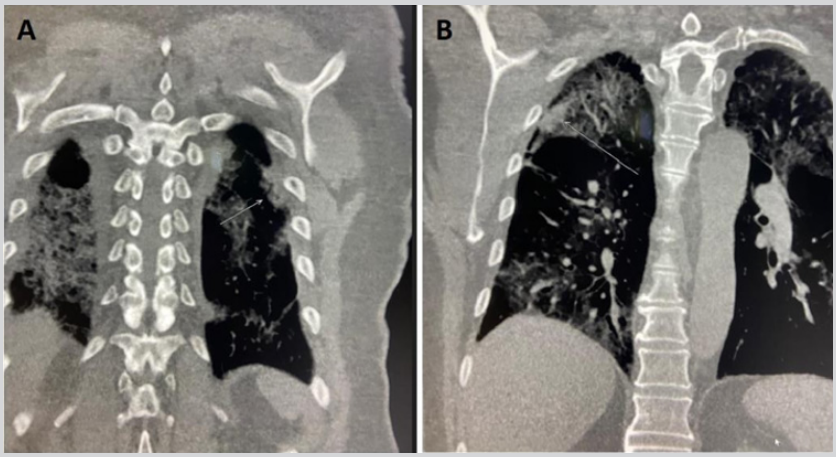

Figure 3: Patient imaging. (A) chest CT in front section. (B) chest CT in front section.

The specific treatment of COVID-19 was started with Tocilizumab 2 days after the patient's admission. It is a monoclonal antibody that inhibits the IL-6 activity, a pro-inflammatory cytokine that plays an important part in the clinical case of the inflammatory syndrome by COVID-19 [9]. Though it was not recommended for routine use in Brazil, Tocilizumab was indicated for those patients hospitalized with COVID-19 in use of MV or HFNC, as well as for those with risks of progressing towards MV, especially in the presence of inflammatory markers [6,10,11]. This way, it is possible to observe that the patient described was in the priority group to receive the medication, having in mind that he was initially in use of low-flow oxygen, but progressed with the need for NRM_2 and a risk of the need for MV. The efficacy of Tocilizumab in COVID-19 patients was evaluated by a variety of scientific studies. A meta-analysis of 27 clinical trials observed that the use of Tocilizumab in patients hospitalized with COVID-19 was associated with lower mortality in 28 days when compared with the placebo or standard treatment branches, though the clinical improvement was not significant in

the general population [12]. Another meta-analysis presented divergent results in regard to the mortality of patients hospitalized with COVID-19, even though it demonstrated a reduction in the risk of mechanical ventilation in this population [13]. Moreover, the effects of Tocilizumab on the increase of survival and the reduction of the time using respiratory support were observed in important clinical trials such as REMAP-CAP [14] and RECOVERY [15].

After the treatment with Tocilizumab, the therapy with Remdesivir was added, an antiviral that inhibits the RNA-dependent polymerase of the SARS-CoV-2, limiting the viral replication of the SARS-CoV-2 [16]. It was initially approved by the European Medicines Agency, and later by the FDA and ANVISA for the treatment of patients with COVID-19 pneumonia and the need for supplementary oxygen, once it showed to reduce the recovery time in this population [17,18]. Though not recommended for routine use in Brazil, in part due to the high costs and low availability [11], the Health Ministry considered the use of Remdesivir as indicated, especially, in the group of patients in the use of low-flow oxygen [10,19]. In the reported case, the drug was started after a desaturation episode that led to the need for HFNC but had a favorable response of good saturation in the use of NIV alternated with HFNC.

The evidence about the use of Remdesivir in COVID-19 justifies its indication in relevant cases, approved by drug regulatory agencies. In the ACTT-117 study, a reduction in recovery time, reduction of progression to mechanical ventilation, and reduction of mortality with the use of Remdesivir were demonstrated in patients hospitalized for COVID-19 using oxygen. However, the SOLIDARITY [20] study did not observe the benefit of the use of Remdesivir for the outcome of mortality in this population. Similarly, a multicenter clinical trial conducted in critically obese patients with COVID-19 showed no benefit in terms of mortality with the use of Remdesivir [21]. Furthermore, in the PINETREE study [22], the early use of Remdesivir determined an 87% reduction in the risk of hospitalization or death in those patients with covid-19 at high risk for unfavorable progression compared to placebo.

Concerning the associated administration of Tocilizumab with Remdesivir, only two clinical trials with divergent conclusions were found [23,24]. One of them showed that the combination of Tocilizumab and Remdesivir was effective in the treatment of patients with severe COVID-19, presenting improvement in pulmonary function parameters and reduction of inflammatory markers [23]. However, the other study demonstrated that the association of Tocilizumab with Remdesivir did not reduce the time of hospitalization in patients with severe COVID-19 pneumonia, when compared to patients who received a combination of placebo with Remdesivir [24]. Therefore, there is an insufficiency of clinical trials in the literature to evaluate this combination of drugs. Finally, it is noted that the results of the literature review about Tocilizumab and Remdesivir, in isolation or in combination, were consistent with the clinical evolution of the patient, suggesting a positive association.

CONCLUSION

The rational use of antivirals and immunomodulators proved to be essential for controlling the COVID-19 pandemic. However, there was a lack of scientific data on the combined administration of Tocilizumab and Remdesivir, despite studies evaluating these drugs separately. In the reported case, the opportune and adequate use of Tocilizumab and Remdesivir was associated with clinical and radiological improvement, avoiding invasive approaches of ventilatory support and, therefore, reducing the fatality risk. It is noteworthy, however, that it is not possible to establish a causal relationship between the favorable clinical evolution of the patient and the use of these drugs.

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CONFLICT OF INTEREST

Eric Bassetti Soares is an employee and stockholder of Gilead Sciences; the other authors claim to have no financial or any other kind of conflict of interest in the making of this case report.

REFERENCES

1. (2020) World Health Organization. Covid-19 Situation Report. World Heal Organ 31(2): 61-66.
2. Cievs R (2022) Avaliação de risco no cenário da covid-19.
3. Umakanthan S, Sahu P, Ranade AV, Bukelo MM, Rao JS, et al. (2020) Origin, transmission, diagnosis and management of coronavirus disease 2019 (Covid-19). Postgrad Med J 96(1142): 753-758.
4. Sharma A, Farouk IA, Lal SK (2021) Covid-19: A review on the novel coronavirus disease. Viruses 13(2): 1-25.
5. Chilamakuri R, Agarwal S (2021) Covid-19: Characteristics and therapeutics. Cells 10(2): 1-29.
6. (2021) Ministério da Saúde. Tocilizumabe para tratamento de pacientes com covid- 19.
7. Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, et al. (2021) Tocilizumab in hospitalized patients with severe covid-19 pneumonia. N Engl J Med 384(16): 1503-1516.
8. Tanni SE, Silvinato A, Floriano I, Bacha HA, Barbosa AN, et al. (2022) Use of remdesivir in patients with COVID-19: a systematic review and meta-analysis. J Bras Pneumol 48(1): 1-13.
9. Alerts S (2022) Tocilizumab: drug information.
10. (2021) Ministério da saúde. diretrizes brasileiras para tratamento hospitalar do paciente com covid-19 - capítulo 2: tratamento farmacológico. Relatório Recom Protoc Clínicos e Diretrizes ter.
11. Kim AY, Gandhi RT (2022) Official reprint from up to date covid-19: Management in hospitalized adults.
12. Sguassero Y, Ch N, Menon S, Tv N, Ferrand G, Kapp P, et al. (2021) Interleukin-6 blocking agents for treating covid-19: a living systematic review.
13. Tleyjeh IM, Kashour Z, Damlaj M, Riaz M, Tlayjeh H, et al. (2020) Efficacy and safety of tocilizumab in covid-19 patients: a living systematic review and meta- analysis. Clin Microbiol Infect 27(8): 1076-1082.
14. (2021) Interleukin-6 receptor antagonists in critically ill patients with covid-19. New England Journal of Medicine. 385: 1147-1149.
15. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, et al. (2021) Tocilizumab in patients admitted to hospital with covid-19(recovery): a randomized, controlled, open- label, platform trial. Lancet 397(10285): 1637-1645.
16. Alerts S, Category P (2022) Remdesivir: drug information.
17. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, et al. (2020) Remdesivir for the treatment of covid-19 Final Report. N Engl J Med 383(19): 1813-1826.
18. European Medicines Agency - EMA. Type II variation assessment report - Veklury. 2020;31(0):51.
19. Brasil M da S do. Ministério Da Saúde Nota Técnica. Dep Gestão e Inc Tecnol e Inovação em Saúde.

20. Repurposed Antiviral Drugs for Covid-19-Interim WHO solidarity trial results. N Engl J Med 384(6): 497-511.

21. Wang Y, Zhang D, Du G, Du R, Zhao J, et al. (2020) Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multi-center trial. Lancet 395(10236): 1569-1578.

22. Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, et al. (202) Early remdesivir to prevent progression to severe covid-19 in outpatients. N Engl J Med 386(4): 305-315.

23. Sarhan RM, Harb HS, Abou Warda AE, Salem-Bekhit MM, Shakeel F, et al. (2022) Efficacy of the early treatment with tocilizumab-hydroxychloroquine and tocilizumab- remdesivir in severe COVID-19 Patients. J Infect Public Health 15(1): 116-122.

24. Rosas IO, Diaz G, Gottlieb RL, Lobo SM, Robinson P, Hunter BD, et al. (2021) Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. Intensive Care Med 47(11): 1258-1270.