Case report

Successful outcome using Tocilizumab in COVID-19 pneumonia with respiratory failure on a ward level

Bianca Codrina Morărașu[1,2,*], Ahmad Basirat[2], Minesh Kooblall[2], Stephen Lane[2]

[1] Department of Internal Medicine and Toxicology, "Sf. Spiridon" Clinical Emergency Hospital, University of Medicine and Pharmacy "Grigore T. Popa" Iasi, Romania; [2]Department of Respiratory Medicine, Tallaght University Hospital, Trinity College Dublin, Ireland

Abstract

We describe the case of a 40-year-old man of Asian ethnicity, who presented with one week history of shortness of breath, productive cough, intermittent hemoptysis, temperature, and systemic symptoms. He had a positive nasopharyngeal swab for SARS-CoV-2, standard COVID panel admission blood tests, a chest X-ray and a CT Pulmonary Angiogram. Significant bilateral infiltrates and no pulmonary embolism were identified. The patient received standard COVID-19 treatment. After 36 hours, he deteriorated requiring initiation of non-invasive ventilatory (NIV) support. In the context of worsening clinical status, the patient received Tocilizumab as a single dose with good clinical response. Early Tocilizumab intervention in appropriately selected patients should improve the outcome and length of hospitalization in COVID-19 pneumonia. It can be used as an intensive therapy unit sparing agent allowing management of critically ill patients on a ward-based level. This may further contribute to prevention of intensive therapy unit related complications and increased mortality.

Keywords: *COVID-19 pneumonitis; Tocilizumab; respiratory failure*

Introduction

Coronavirus disease 2019 (COVID 19) has rapidly evolved into a global emergency. It is caused by a highly contagious single stranded RNA virus. Although new variants emerge and the natural evolution of the infection changes, there is still a major pressure on the medical system, particularly intensive care units [1].

Clinical presentation ranges from asymptomatic to severe pneumonia with potential acute respiratory distress syndrome (ARDS) leading to high mortality. This is triggered by the inflammatory storm generated by IL-6 among other cytokines. It leads to a sequence of events which causes pyrexia, lymphopenia, lung injury and multi-organ failure. Increasing research has focused on the potential role of inhibiting IL-6 production [2]. Tocilizumab is an anti-IL6 receptor monoclonal antibody which has shown to reduce the inflammatory reaction, improve imagistic changes, and decrease the likelihood of ventilatory support in patients with COVID 19 infection [3]. We present the case of an Asian patient with severe COVID 19 pneumonitis and respiratory failure who was trialed at ward level on Tocilizumab as an additional agent to standard therapy. As it appears that Asian individuals have a higher risk of COVID-19 infection, intensive therapy unit (ITU) admission and possibly death [4], our case report represents the foundation for future therapeutic options to prevent ITU admission.

Received: February 2022; Accepted after review: March 2022; Published: March 2022.

*Corresponding author: Bianca Codrina Morărașu, Department of Internal Medicine and Toxicology, University of Medicine and Pharmacy "Grigore T. Popa" Iasi, 16 Universitatii str., Iasi, Romania
Email: morarasu.bianca.codrina@gmail.com

Case report

A 40-year-old man of Asian ethnicity, originally from Pakistan, presented to the emergency department with one week history of sore throat, productive cough of yellow sputum and intermittent hemoptysis, shortness of breath, temperature, generalized myalgia, headache, vomiting and diarrhea. The patient had a positive nasopharyngeal swab for SARS-CoV-2, 1 day prior to admission. There was no significant past medical or smoking history. Clinical examination showed inferior to mid zone bilateral lung crepitations, and hypoxemwith a PaO2 of 6.81 kPa on arterial blood gas. The patient had standard COVID panel admission blood tests, a chest X-ray and a CT Pulmonary Angiogram in order to rule out concomitant pulmonary thromboembolism. Significant bilateral pulmonary infiltrates (Figure 1A) and no pulmonary embolism were identified.

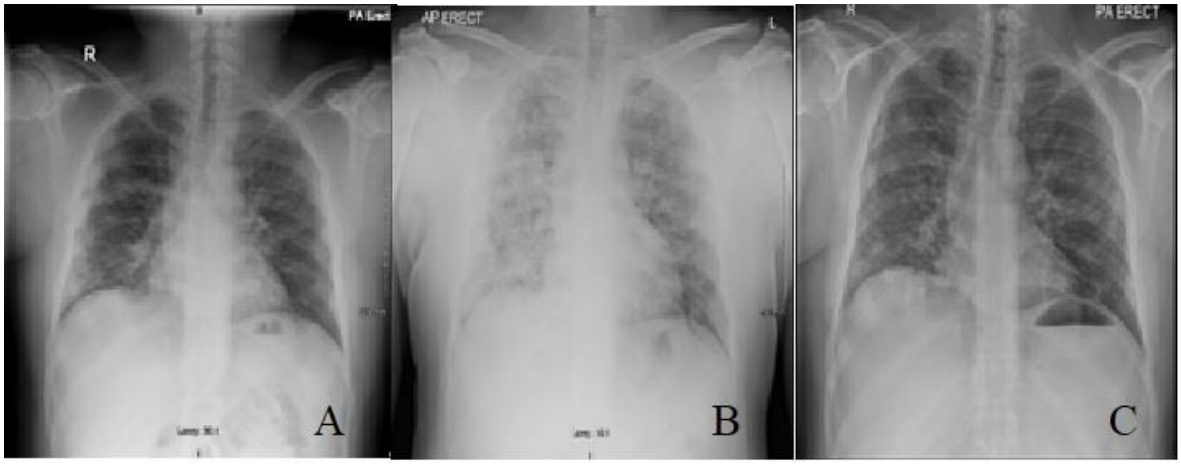

Fig. 1. A- chest x-ray with bilateral pulmonary infiltrates; B- chest x-ray with worsening bilateral pulmonary infiltrates; C- chest x-ray with significant resolution of the bilateral infiltrates.

On admission, the patient received standard dose of antibiotics, oral dexamethasone, and prophylactic low molecular weight heparin. He was stable for the first 36 hours with SpO2 96% on 2L O2 via nasal cannula. Subsequently, he became suddenly hypoxic, pyrexic, tachypneic, requiring initiation of non-invasive ventilatory (NIV) support. We repeated the chest x-ray (Figure 1B). He was started on AirVo 30 L O2, FiO2 60%, but shortly required further escalation to continuous positive airway pressure (CPAP), PEEP of 8, FiO2 60%. In the context of worsening clinical status, imagistic and paraclinical markers, the patient received 8mg/kg of Tocilizumab as a single dose. We continued with NIV for another 3 days, but progressively weaning off. By day 4 after Tocilizumab, there was a significant improvement in the shortness of breath at rest and the SpO2 was >94 % with O2 delivered through nasal cannula.

The patient maintained room air saturation by day 10 after Tocilizumab.Prior to discharge, we repeated a chest x-ray and there was significant resolution of the bilateral inflammatory infiltrates (Figure 1C).

The blood tests confirmed the clinical and imagistic improvement of the COVID-19 infection with a significant drop in inflammatory markers (Table 1). IL-6 was significantly raised but starting to improve 72 hours post Tocilizumab. It had another peak on day 7 of admission, but at this stage, the patient was clinically stable (Figure 2).

Table 1. Blood tests showed lymphopaenia and raised inflammatory markers, including IL-6, ferritin, D-dimers and CRP.

Tocilizumab treatment	24 hours prior	72 hours after
White cell count	7.5* 103/µL	7.1* 103/µL
Neutrophils	6.2* 103/µL	5.4* 103/µL
Lymphocytes	0.7* 103/µL	1.2* 103/µL
Platelets	168* 103/µL	341* 103/µL
Ferritin	2171 µg/l	855 µg/L
Procalcitonin	1 ng/mL	0.2 ng/mL
IL-6 level	188 pg/mL	112 pg/mL
CRP	282 mg/dL	36 mg/Dl
LDH	459 U/L	347 U/L
D-dimers	1.07 µ/mL	1.29 µ/mL

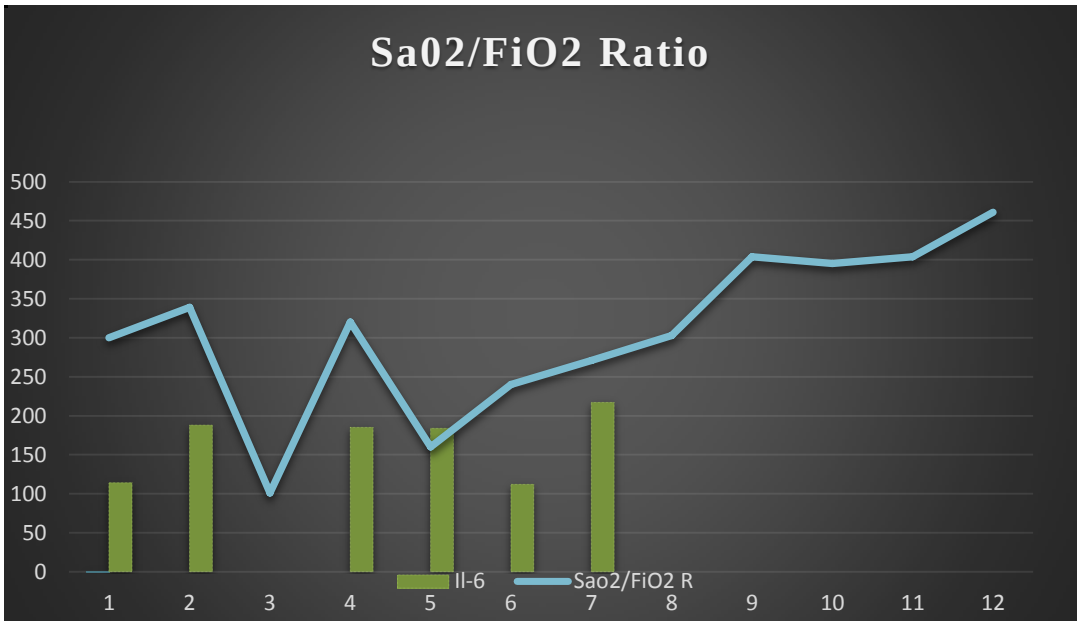

Fig. 2. SaO2/FiO2 ratio from day 1 to day 12 of admission. Green bars represent IL-6 level throughout admission. Blue arrow indicates day of Tocilizumab administration.

Discussions

It is widely known that patients with severe COVID-19 infection develop an exaggerated immune response. Together with other innate immune cells, there is a pro-inflammatory reaction widely known as the cytokine storm or cytokine release syndrome (CRS) [5]. It has been shown to directly correlate with the severity of the infection, lung injury and multi-organ failure [1]. SARS-CoV-2 activates the innate and adaptive immune system in the alveolar epithelial cells. This results in a cascade of inflammatory events leading to accumulation of fluid and reactive cells expressed clinically as shortness of breath with potential to determine respiratory failure and acute respiratory distress syndrome (ARDS) [6]. The initial clinical presentation of our patient was consistent with pneumonitis. More important was the sudden onset and rapid respiratory deterioration requiring significant ventilatory support suggesting development of CRS. This is a critical moment as previous studies showed that Asians are at higher risk of infection, admission in intensive therapy unit and death [4].

Three of the main cytokines involved in this inflammatory reaction are IL-1, IL-6 and TNF-α. IL-6 is a key player in the cytokine

storm. It is involved in the acute phase response, with effects on the T and B cell population, as well as implications in vascular and metabolic activity [7]. Our patient had elevated levels of IL-6. It peaked as the patient's clinical status deteriorated and oxygen needs increased. This observation was made in several previous studies as IL-6 may be a good prognostic marker for progression to severe disease and to predict a negative outcome [8].

Tocilizumab is an IgG1 subtype monoclonal antibody which binds to IL-6 receptor. It has been previously used in rheumatologic and other inflammatory conditions [9] as well as in patients with SARS-CoV-2 infection and evidence of cytokine storm [10].

Guidelines for inclusion criteria were patients with microbiological confirmation of COVID-19 infection, evidence of bilateral lung infiltrates on the chest x-ray, SpO2 ≤ 93%, and/or PaO2/FiO2 ratio < 300 mmHg, established presence of hyperinflammation through biologic parameters and no other superimposed acute infection. Our patient received Tocilizumab in the first 12 hours of clinical deterioration. We consider that early intervention should suppress the inflammatory cascade and its associated complications. In the trial done by Salvarani et all, Tocilizumab was given within 8 hours or less of patient randomization. Although the trial was stopped early due to lack of evidence in achieving primary outcome, they reported a significantly reduced overall mortality of 2.4% [11].

The RECOVERY trial showed that use of dexamethasone in patients hospitalized with COVID-19 lowered the 28th day mortality in those receiving oxygen therapy or mechanical ventilation [12]. Our patient received both oral Dexamethasone as part of the standard therapy and the Tocilizumab infusion. This is supported by the REMAP-CAP trial which showed clear benefit from Tocilizumab, including survival, in patients with COVID-19 receiving organ support in ICU [13].

In our care report, there was a clear therapeutic benefit as we prevented intensive therapy unit admission. The rapid clinical deterioration took a positive turn after Tocilizumab infusion with marked improvement of the clinical and inflammatory markers, as well as O2 requirements within 3 days of Tocilizumab. Another trial confirmed similar outcomes. The CORIMUNO-19-TOCI-1 trial included patients with COVID-19 pneumonia requiring a minimum of 3L flow oxygen treated with Tocilizumab. It showed improved survival without the need for NIV or mechanical ventilation by day 14. However, the 28-day overall mortality rate was 11.5% [14] with the COVACTA trial that showed no clinical improvement or reduced mortality at 28 days [15].

Another retrospective case series looked at the mortality rate in 61 patients with severe COVID-19 pneumonia admitted in ICU. They added Tocilizumab to their standard treatment which also included Dexamethasone. Unfortunately, the case series did not find any mortality benefit of Tocilizumab in this category of patients [16], finding supported by Stone et all [17] which did not find any benefit from Tocilizumab in preventing intubation. Compared to most of the trials, they used moderately ill patient cohort in contrast with Rojas et all which found that Tocilizumab treatment was associated with a lower mortality, but when intubated patients were excluded [18].

Conclusions

Although data is conflicting, we are of opinion that early Tocilizumab intervention in appropriately selected patients should considerably improve the outcome and length of hospitalization in COVID-19 pneumonia. Most importantly, it can be used as an ITU sparing agent allowing management of critically ill patients on a ward-based level. This may further contribute to prevention of ITU related complications and increased mortality.

Acknowledgements

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflicts of interest

The authors declare that they have no competing interests.

References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395(10223): 497–506. doi:https://doi.org/10.1016/S0140-6736(20)30183-5
2. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. *N Engl J Med.* 2021; 384(1):20-30. doi: 10.1056/NEJMoa2030340.
3. Alattar R., Ibrahim TBH, Shaar SH, et al. Tocilizumab for the treatment of severe COVID-19. *J Med Virol*. 2020; 92(10):2042-2049. doi: 10.1002/jmv.25964.
4. Sze S, Pan D, Nevill CR, et al. Ethnicity and clinical outcomes in COVID-19: A systematic review and meta-analysis. *EClinicalMedicine*. 2020; 29:100630. doi: 10.1016/j.eclinm.2020.100630.
5. Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate Coronavirus Disease 2019. *J Clin Invest*. 2020; 130(5):2620–2629. doi: 10.1101/2020.02.16.20023903.
6. Leiva-Juarez MM, Kolls JK, Evans SE. Lung epithelial cells: therapeutically inducible effectors of antimicrobial defense. *Mucosal Immunol*. 2018; 11(1):21–34. doi: 10.1038/mi.2017.71.
7. Hunter CA., Jones SA. IL-6 as a keystone cytokine in health and disease. *Nat Immunol*. 2015;16(5):448–457. doi: 10.1038/ni.3153. Erratum in: Nat Immunol 2017; 18:1271.
8. Grifoni E,Valoriani A, Cei F, et al. Interleukin-6 as prognosticator in patients with COVID-19. *J Infect*. 2020; 81(3): 452–482. doi: 10.1016/j.jinf.2020.06.008.
9. Navarro G, Taroumian S, Barroso N, Duan L, Furst D. Tocilizumab in rheumatoid arthritis: a meta-analysis of efficacy and selected clinical conundrums. *Semin Arthritis Rheum*. 2014; 43(4):458–469. doi: 10.1016/j.semarthrit.2013.08.001.
10. Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN. Pharmaco-Immunomodulatory Therapy in COVID-19. *Drugs*. 2020;80(13):1267-1292. doi: 10.1007/s40265-020-01367-z.
11. Salvarani C, Dolci G, Massari M, et al; Effect of tocilizumab vs standard of care on clinical worsening in patients hospitalized with COVID-19 pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2020; 81(1):24-31. doi: 10.1001/jamainternmed.2020.6615.
12. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021; 384(8):693-704. doi: 10.1056/NEJMoa2021436.
13. Angus DC, Berry S, Lewis RJ, et al. The REMAP-CAP (Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia) Study. Rationale and Design. *Ann Am Thorac Soc*. 2020;17(7):879-891. doi: 10.1513/AnnalsATS.202003-192SD.
14. Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. *JAMA Intern Med*. 2021;181(1):32-40. doi: 10.1001/jamainternmed.2020.6820. Erratum in: JAMA Intern Med. 2021;181(1):144. Erratum in: JAMA Intern Med. 2021;181(7):1021.
15. Furlow B. COVACTA trial raises questions about tocilizumab's benefit in COVID-19. *Lancet Rheumatol*. 2020; 2(10):e592. doi: 10.1016/S2665-9913(20)30313-1.
16. Mady A, Aletreby W, Abdulrahman B, et. Al. Tocilizumab in the treatment of rapidly evolving COVID-19 pneumonia and multifaceted critical illness: A retrospective case series. *Ann Med Surg (Lond).* 2020; 60:417-424. doi: 10.1016/j.amsu.2020.10.061.
17. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Tocilizumab Trial Investigators. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. *N Engl J Med.* 2020;383(24):2333-2344. doi: 10.1056/NEJMoa2028836.
18. Rojas-Marte G, Khalid M, Mukhtar O, et al. Outcomes in patients with severe COVID-19 disease treated with tocilizumab: a case-controlled study. QJM. 2020; 113(8):546-550. doi: 10.1093/qjmed/hcaa206. Erratum in: QJM. 2021 Jan 14:null.