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The Use of Tocilizumab in COVID-19 Positive Patients: Initial Outcomes in 2 Patients

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Abstract

Introduction: The recent pandemic that has been caused by the novel coronavirus, SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronovirus-2) has led to a huge burden on health, social and economic systems worldwide. There is currently no known cure. The medical fraternity is left to care for large numbers of ill patients using treatments that have not been clinically proven to be effective. The rapid spread of the virus has not allowed for large scale clinical trials to be undertaken and thus most treatment regimens have been based on observational studies. Tocilizumab has shown promise in some reports when used in the hyper inflammatory stage of the disease.

Methods: Two patients who were Intensive Care Unit (ICU) requiring were administered 400 mg of Tocilizumab as a single dose after having been diagnosed with features of a Cytokine Release Syndrome.

Results: Both patients responded positively with a decrease in symptomatology and inflammatory markers.

Conclusion: Patients who present in the hyper-inflammatory stage of SARS-CoV-2 may be considered for Intravenous (IV) Tocilizumab therapy.

Keywords: Tocilizumab • SARS-CoV-2 • Medical fraternity

Introduction

As of 26 April 2020, the World Health Organization reported 2804796 confirmed global cases of COVID-19 with 193 710 deaths attributed to the disease [1]. South Africa was reported to have 4361 confirmed cases with 86 deaths. The social and economic burden of this pandemic is unprecedented. Multiple lives have been lost and healthcare systems have been overwhelmed. The mortality rate of COVID-19 is estimated to be 3.7% (World Health Organisation) which is ten times higher than the mortality seen with the seasonal influenza virus. The spectrum of disease varies widely from patients who are completely asymptomatic, to those who require mechanical ventilation. An initial study from the United Kingdom revealed that two thirds of COVID-19 patients admitted to the Intensive Care Unit (ICU) needed mechanical ventilation within the first 24 hours [2]. In the Seattle region of the United States, 75% of COVID positive patients admitted required mechanical ventilation [3]. In a resource constrained country such as ours it is imperative to use all available means to limit the number of patients requiring mechanical ventilation.

A key feature in those who progress to mechanical ventilation may be the development of a cytokine storm with features of a Cytokine Release Syndrome (CRS) and Macrophage Activation Syndrome (MAS) resulting in ARDS. This results in the increase in several circulating inflammatory cytokines among them being Interleukin (IL) 6 and the presence of elevated levels of ferritin, d-dimer and low platelets. The clinical signs and symptoms associated with CRS are variable of which fever tends to be a central component. Other symptoms include malaise, fatigue, nausea and vomiting, tachycardia, hypotension, elevated D-Dimer, azotemia, hepatic transaminitis and changes in mental state [4]. Tocilizumab (TCZ) is an anti-IL-6 Receptor blocker which has been previously approved for the therapy of CRS and is currently being investigated as a form of treatment for severe COVID-19 patients who develop CRS and ARDS.

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Method

Two patients infected with COVID-19 were admitted to the intensive care unit for treatment. Both patients received a single dose of IV TCZ (400 mg) in addition to the standard of care of treatment.

Case Series

Case 1

A 52-year-old gentleman, with a background of hypertension and dyslipidaemia, presented to his General Practitioner (GP) on the 14th April 2020 with a cough and mild shortness of breath. His chronic therapy included amlodipine 5 mg daily, enalapril 10 mg daily and rosuvastatin 10 mg daily. He had no recent travel history and no contact with a positive COVID-19 individual. His GP proceeded to do a nasopharyngeal swab and submitted it for COVID-19 PCR. A blood panel was ordered by the GP during the same visit which showed an elevated C-Reactive Protein (CRP) of 164.5 mg/L, a normal White Cell count (WCC), a normal Erythrocyte Sedimentation Rate (ESR) of 32 with an elevated Ferritin of 1 998 ng/mL with an elevated Alanine Amino Transferase (ALT) and Aspartate Amino Transferase (AST) of 89 IU/L and 98 IU/L respectively. A Chest radiograph undertaken on the same day revealed right medial basal opacification with coarse peri-hilar broncho-vascular markings and peri-bronchial thickening. He was commenced on Moxifloxacin, Montelukast and a Budesonide/Formoterol inhaler by his GP while awaiting the results of his investigations. He was sent home to continue with treatment.

The following morning his condition had deteriorated and he was referred by the GP for hospitalisation. Upon arrival he was found to be hypoxic on room air with a saturation of 86%. He was admitted to the High care isolation unit and commenced on prophylactic antibiotics and supplemental oxygen at 2 l/min. His COVID-19 PCR swab result was pending at the time of admission and a decision was taken to commence the patient on corticosteroid therapy (Solumedrol 40 mg twice daily IV), prophylactic antibiotics (Amoxicillin/

Clavulanic acid 1.2 g 8 hourly IV and Azithromycin 250mg IV daily) and a prophylactic dose of Enoxaparin (60 mg administered subcutaneously every day). The following day his COVID-19 PCR returned as positive and Chloroquine 400 mg daily per os, Zinc supplementation, Vitamin C 1g twice daily and Vitamin D 50000 IU stat were added to his therapy. His CRP was repeated which stood at 179.5 mg/L with a WCC of 10.8 (marginally elevated). His lymphocyte percentage was 12.7% (below normal).

At this stage he developed diarrhoea, for which he was treated symptomatically. A stool sample for Clostridium difficile was sent off which was negative. The patient's condition continued to deteriorate with a worsening PaO_2/FiO_2 (P/F) Ratio <250 as well as a pyrexia approaching 40-degree Celsius. A diagnosis of Cytokine-Release Syndrome was thus considered. A decision was made to start TCZ and a single dose of 400 mg IV was administered whilst continuing with the previously scripted corticosteroid. The patient made a dramatic recovery by the following morning (18 April 2020) with compete resolution of the pyrexia as well as an improvement in his CRP and ferritin levels (51.5 mg/L and 1047 ng/mL respectively). A D-Dimer was performed which was within the normal range (0.43 mg/L). The patient's lymphocyte percentage had dropped slightly to 10.5%. He continued to improve and was transferred to the ward on the 21 April 2020. At this stage he had completed 5 days of Chloroquine and his dose of methylprednisolone was decreased to 40 mg daily. He spent a further 3 days in hospital during which time he was weaned off his supplemental oxygen and subsequently discharged home on the 24 April 2020. A repeat COVID-19 PCR performed on the 23 April 2020 returned negative. A telephonic consult undertaken on the 25 April 2020 revealed no new concerns (Figure 1).

Case 2

A 54-year-old female, with no known co-morbidities, presented to her local emergency department on the evening of the 18 April 2020 with respiratory distress. She required intubation which was performed by the casualty doctors. The attending hospital did not have any available ICU beds and she was transferred to our facility. Her diagnosis on the transfer letter was stated as cardiac failure. She was admitted into the isolation unit at our facility. Her CXR Figure 2 was suspicious for a possible COVID-19 infection with bilateral ground glass opacification or an atypical pneumonia (Pneumocystis pneumonia was considered). Her initial COVID-19 PCR screen, which was performed at the referring facility, was negative. A CT of the chest revealed bilateral ground glass attenuation and consolidation (Figure 3). The initial blood tests taken showed renal dysfunction with a urea of 9.1 mmol/L and a creatinine of 188 *u*mol/L. She was commenced on a low dose of Noradrenalin in order to augment blood pressure. Antibiotic therapy (Amoxicillin/Clavulanic acid 1.2 g 8 hourly IV and Azithromycin 250 mg IV daily) and glucocorticoids (Hydrocortisone 100 mg 8hrly IVI) were also started. Significant liver dysfunction was noted with an

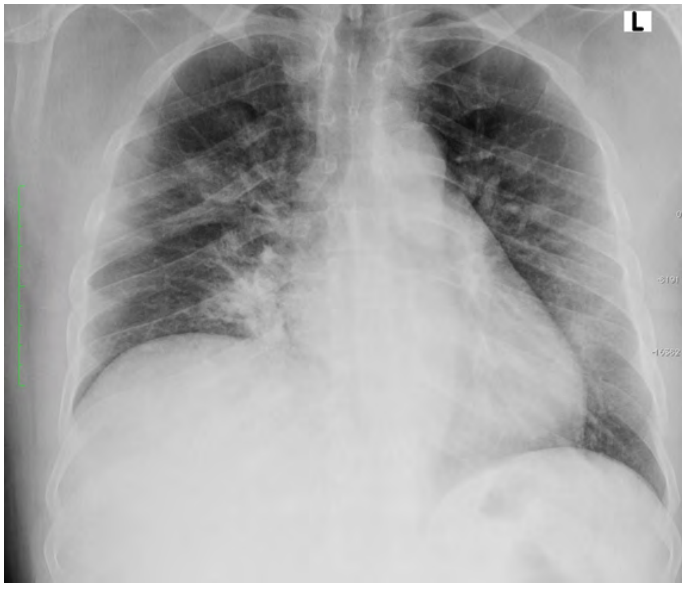

Figure 1. Chest radiograph (L).

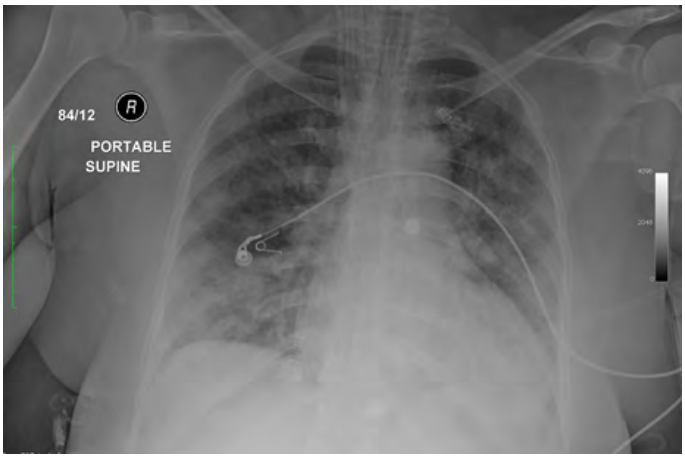

Figure 2. Chest radiograph portable supine (R).

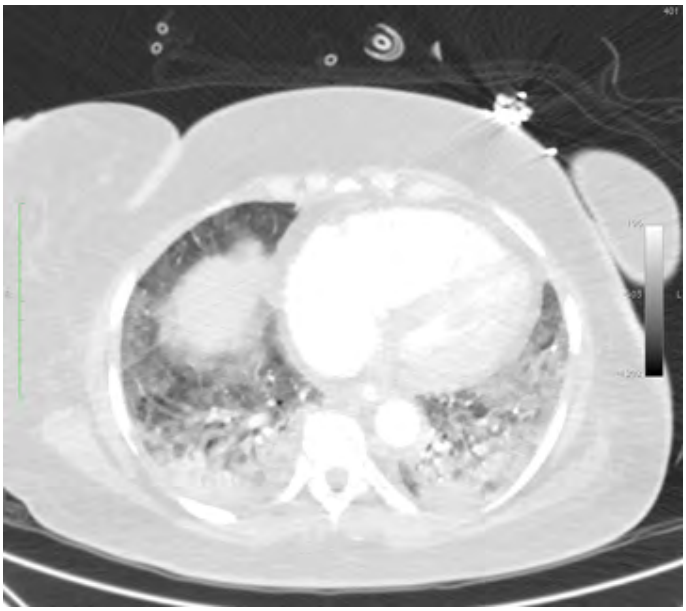

Figure 3. Computed tomography of chest.

ALT and AST of 1 711 IU/L and 2 508 IU/L respectively and an INR of 2.6. She had an elevated troponin of 870 ng/L and a CRP of 131.5 mg/L with a PCT of 4.62 ng/mL.

An elevated ferritin of 15 612 *ug*/L was recorded with a beta-2-Microglobulin of 4.16 mg/L. Her full blood count showed a haemoglobin of 11.9 g/dL, a decreased platelet count of 127 and a decreased lymphocyte percentage of 12.1%. A fungi tell subsequently returned as 34 pg/mL. An initial cardiac echo was performed which revealed a normal left ventricular ejection fraction with right ventricular strain. Her connective tissue screen revealed a low positive ANA of 1:80 and a hepatitis screen was negative. The renal function continued to deteriorate and she was started on Continuous Veno-Venous Haemodiafiltration (CVVHDF) upon admission to the unit. A repeat COVID-19 PCR was performed on tracheal aspirates and was positive. She was commenced on Chloroquine 400 mg bd and Zinc supplementation. The hydrocortisone was switched to methylprednisolone 40 mg twice daily IV. Vitamin D (50000 IU stat) and Vitamin C (1 g twice daily) were also started. She also received TCZ (400 mg IV stat) 400 as she was deemed to be in a hyper inflammatory state. Ventilation was continued (SIMV; PSV 18 cm; PEEP 12 cm; FiO_2 (0.6) and CVVHDF was maintained. The patient's condition improved within 24 hours of the change in therapy. A decline in the CRP was noted (27.6 mg/L). Her ventilation was subsequently weaned. The liver function test continued to improve with the ALT and AST decreasing to 1 494 IU/L and 793 IU/L respectively. Her renal function improved and she was extubated using the Alfred ICU Guideline. The patient remained on supplemental oxygen (2 l/

min) as of the 25 April 2020 and continues to clinically improve.

Discussion

A previous open label, non-controlled, non-peer reviewed study in China looked at 21 patients with severe ARDS secondary to COVID-19 to whom TCZ was administered. The majority of these patients improved with lower oxygen requirements and improving lymphocyte counts noted. Nineteen of the 21 patients were discharged with a mean of 15.5 days after TCZ treatment [5]. Further local experience was noted with the administration of TCZ to a patient in a Johannesburg intensive care unit resulting in marked improvement of biomarkers and hypoxaemia. Subsequently, mechanical ventilation was avoided with the patient discharged 4 days after the initial dose of TCZ [6]. However, there is currently a dearth of data regarding outcome after the use of TCZ in COVID-19 patients. The timing of TCZ administration appears to be an important factor in outcome. If the drug is administered too early there is a risk of further immune suppression resulting in increased viral replication. However, if it is administered too late, there is a risk of the inflammatory cascade worsening. A case report of 2 patients receiving TCZ and having poor outcomes highlighted the need for randomised clinical trials. This is required in order to establish the proper period within the disease course to administer TCZ and the outcomes thereof [7]. There are currently multiple clinical trials which are recruiting adult patients to determine safety and efficacy of TCZ in the treatment of severe COVID-19 pneumonia. Currently, TCZ is not registered by the MCC for COVID-19 treatment. However, the Monitored Emergency use of Unregistered and Investigational Interventions (MEURI) is an ethical protocol developed by the WHO to evaluate the potential use of experimental drugs during public health emergencies under which the use of TCZ will be permitted in South Africa. This will require a number of criteria to be met viz. expert panel involvement prior to prescription, detailed patient data collection, and the meeting of strict inclusion and exclusion criteria [8].

Conclusion

Our case report reinforces the need for further evidence with regards to the usage of TCZ. Randomised controlled trials with TCZ will be of extreme importance in establishing proper guidelines with regards to its usage in severe COVID-19 infections. Awareness and diagnosis of the Cytokine Release Syndrome appears to be paramount in determining the timing of TCZ administration. South Africa is a country with severe resource constraints. A significant percentage of our population, with its burden of both communicable and non-communicable disease are considered to be at high risk for developing severe COVID-19 disease. It is imperative that we explore all options which may reduce both the morbidity and the need for prolonged intensive care treatment for patient's diagnosed with severe COVID-19 disease.

Teaching Points

- Important to diagnose the hyper-inflammatory state (CRS) of COVID-19 infections.
- Discussion of cases with a panel before administration of tocilizumab.
- Appropriate timing of tocilizumab administration appears to be vital in achieving better outcomes.

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