

Clinical benefits of Tocilizumab in COVID-19-related cytokine release syndrome in a patient with end-stage kidney disease on haemodialysis in Australia

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Abstract

COVID-19 remains a global pandemic with more than 10 million cases and half a million deaths worldwide. The disease manifestations in patients with chronic kidney disease and especially those on haemodialysis are still being understood, with only a few overseas case series, and small observational trials thus far. It appears that the disease is more severe in this patient cohort. Part of the pathophysiology of severe COVID-19 is related to accompanying cytokine release syndrome (CRS). Tocilizumab, an interleukin-6 inhibitor, has been trialled for treatment of CRS in COVID-19, but not yet approved. We present a case of an Australian patient on long-term haemodialysis with severe COVID-19 who was successfully treated with Tocilizumab. The peak of her illness was on day 7, with a C-reactive protein of 624 mg/L (reference < 5 mg/L), ferritin of 5293 ng/mL (reference 30-500 ng/mL), and interleukin-6 level 1959.7 pg/mL, consistent with CRS. She was severely hypoxic on a ventilator, with rising inotropic requirements. With the use of Tocilizumab, there was a significant and immediate response in her inflammatory markers, and she made a steady recovery. The patient was discharged home 6 weeks after presentation.

KEYWORDS

chronic, coronavirus, cytokine release syndrome, dialysis, interleukin-6, kidney failure

1 | CASE

A 72-year-old woman reported a 24-hour history of dry cough, rhinorrhoea, and myalgias during routine attendance for haemodialysis for end-stage kidney disease secondary to autosomal dominant polycystic kidney disease at a hospital dialysis unit in Melbourne, Australia in March 2020. The patient had been dependent on haemodialysis for 18 months and active on the kidney transplant list prior to presentation. Her other medical history includes a chronically elevated hemidiaphragm, paroxysmal atrial fibrillation on amiodarone, hypertension, dyslipidaemia and an inguinal hernia repair 2 weeks prior.

At the time of presentation (day 0), she was found to have thrombosis of her arteriovenous fistula (AVF) and was unable to undergo

dialysis. She was admitted to hospital and underwent a surgical revision of the fistula that evening.

Despite her upper respiratory tract symptoms, the patient appeared well, was afebrile, and all her vital signs were within normal limits. She reported no epidemiological criteria for COVID-19, including no close contact with a confirmed case or recent travel, but received a nasopharyngeal swab for COVID-19 as part of theatre protocol.

The next evening, she spiked a fever of 39.4°C and was commenced on intravenous Ceftriaxone and Azithromycin for a community-acquired pneumonia. On day 2, while undergoing dialysis through her revised fistula, she had more fevers associated with rigors and complained of severe 'bone pain'. Her antibiotics were changed to intravenous Piperacillin-Tazobactam, Azithromycin, and Vancomycin to

cover for possible bacteraemia post-AVF revision. She was lymphopaenic at $0.4 \times 10^9/L$ (reference $1.0-3.5 \times 10^9/L$), and C-reactive protein (CRP) was 80 mg/L (reference $<5 \text{ mg/L}$). Influenza A/B, respiratory syncytial virus and rhinovirus polymerase chain reaction (PCR), urine atypical pneumonia screen, serial blood cultures and urine were unremarkable. Chest radiograph revealed mild left perihilar interstitial type opacity as well as left upper lobe opacity consistent with developing consolidation (Figure 1A). That evening, the patient became hypoxic, with oxygen saturations dropping to 89% on room air, febrile at 40.3°C , and hypotensive with a blood pressure (BP) of 87/50 mm Hg (baseline systolic BP around 110 mm Hg). She was transferred to the intensive care unit (ICU) for inotropic support.

Two severe acute respiratory syndrome coronavirus 2 (SARS-COV2) PCR swabs returned positive and the patient clinically

SUMMARY AT A GLANCE

A report of an elderly long-term haemodialysis patient who successfully recovered from a cytokine release syndrome due to severe COVID-19 using an IL-6 inhibitor, tocilizumab.

deteriorated rapidly requiring intubation on day 6 of admission, at which time nasogastric feeds were also commenced. Chest radiographs demonstrated rapid daily progression and increased volume of bilateral extensive consolidation with sub-pleural sparing, suggestive of acute respiratory distress syndrome (ARDS) (Figure 1B). Around

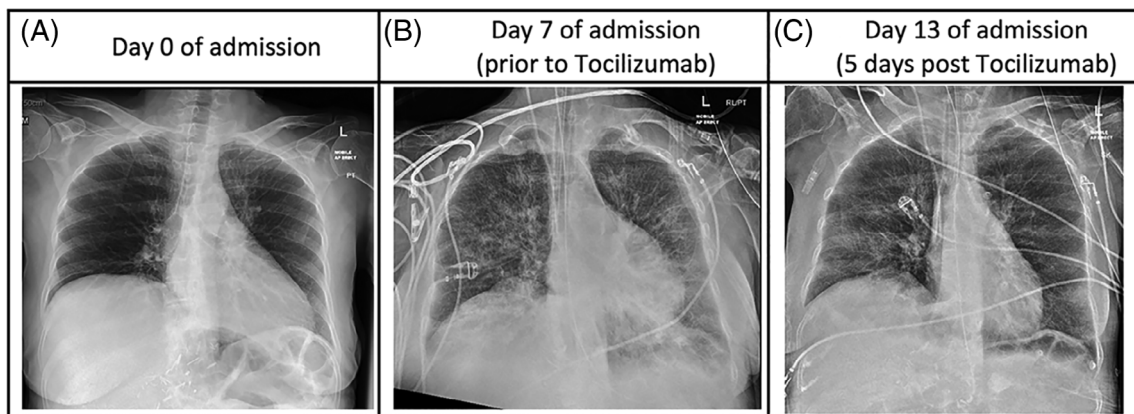


FIGURE 1 A series of anterior-posterior radiographs of the patient's chest demonstrating development of ARDS in the setting of cytokine release syndrome in severe COVID-19 infection and significant improvement post-Tocilizumab. A, Mild increase in left upper lobe opacity consistent with developing consolidation on day 0 of admission. B, Bilateral extensive consolidation and interstitial opacities with sub-pleural sparing suggestive of ARDS on day 7 of admission prior to Tocilizumab. C, Improving interstitial and airspace changes on day 13 of admission, 5 days post-Tocilizumab

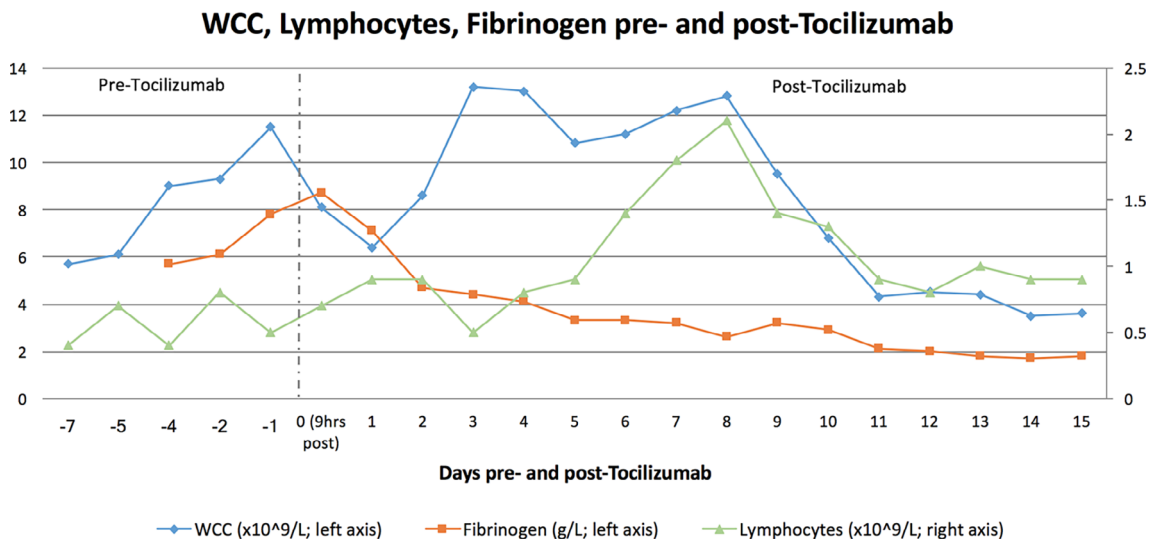


FIGURE 2 A scatter graph of the patient's pathology results; WCC, lymphocytes and fibrinogen comparing pre- and post-administration of Tocilizumab [two doses of 8 mg/kg (450 mg) IV administered 12 hours apart] on day 0. WCC, white cell count

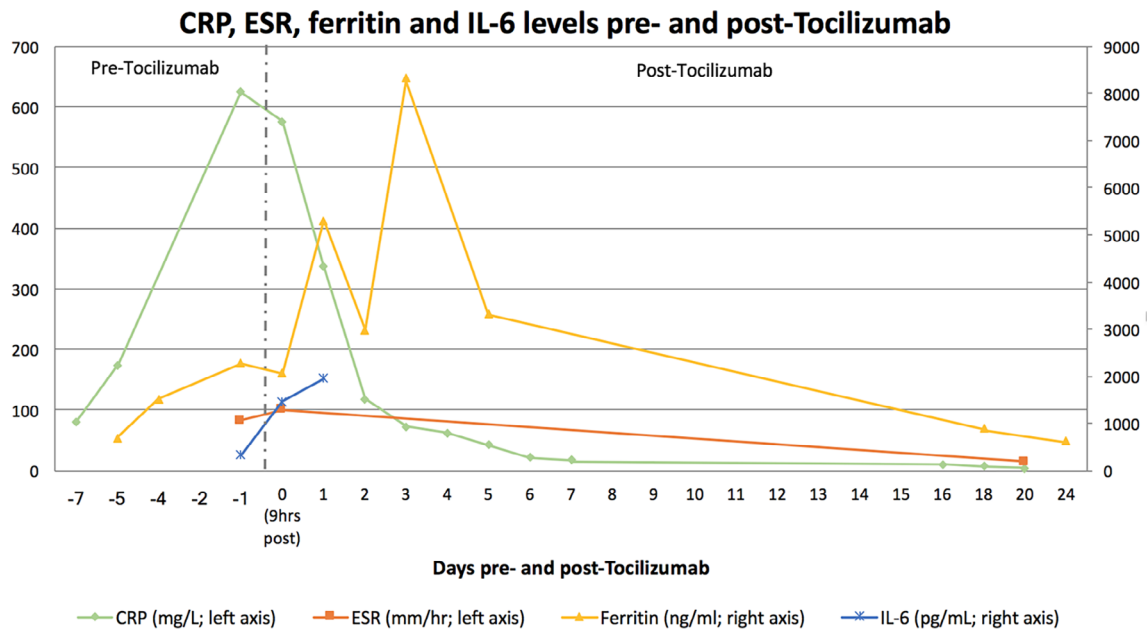


FIGURE 3 A scatter graph of the patient's pathology results; CRP, ESR, ferritin and IL-6 levels comparing pre- and post-administration of Tocilizumab [two doses of 8 mg/kg (450 mg) IV administered 12 hours apart] on day 0. CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6

day 7 of admission, her CRP rose to 624 mg/L (reference <5 mg/L), erythrocyte sedimentation rate was >100 mm/h (reference 5-20 mm/h), interleukin-6 (IL-6) level was significantly elevated at 1959.7 pg/mL (reference 0.0-149.0 pg/mL), ferritin was 5293 ng/mL (reference 30-500 ng/mL), fibrinogen 7.8 g/L (reference 2.0-4.5 g/L) (Figure 2, Figure 3) and she desaturated to 73% on 100% supplemental oxygen at 40 L/min with positive end-expiratory pressure of 15cmH₂O. The clinical picture and investigation results were consistent with cytokine release syndrome (CRS) and the patient was critically ill.

After a multi-disciplinary discussion involving the Renal, Haematology, Infectious Diseases and ICU teams, she was administered two doses of Tocilizumab 8 mg/kg (450 mg) intravenously 12 hours apart as well as Hydroxychloroquine 400 mg twice a day. The latter was ceased 3 days later due to QTc prolongation (490 ms). She was also commenced on Nitric Oxide up to 40 ppm and prone positioning was used for 12 to 16 hours from day 8. At the peak of her inotropic supports, the patient required 30 mg/h of Noradrenaline with 2.4 units/h of Vasopressin to aim for a mean arterial pressure of 65 mm Hg. While the initial target for fluid balance was negative 3 L, this could not be achieved without further incrementing the inotropic requirement. Thus, the aim was changed to an even balance, but even this was proving challenging despite continuous veno-venous haemodiafiltration.

At 9 hours post the first Tocilizumab dose, the CRP had already fallen from 624 to 576 mg/L. Within 72 hours (day 11), the CRP fell to 72 mg/L (Figure 3), oxygenation improved to 96% with FiO₂ 30% and oxygen flow of 50 L/min, and sedation was able to be weaned off. Inotropic supports were weaned off on day 18, and the patient was extubated. She was discharged from ICU to the ward on day 21, saturating at 99% on 2 L of oxygen by nasal prongs. Other minor

issues during the ICU admission included anaemia requiring intermittent blood transfusion in the setting of withheld erythropoietin stimulating agent, and the development of a stage 1 heel pressure ulcer.

On discharge to the ward, she required physiotherapy and alternate-daily haemodialysis with BP support using pre-dialysis Midodrine at 5 mg and 20% concentrated albumin for fluid overload. The patient walked out of hospital 6 weeks post admission, and has had two negative COVID-19 PCR tests 8 weeks from her initial positive result.

2 | DISCUSSION

COVID-19 caused by SARS-COV2 has affected more than 10 million cases with 500 000 deaths worldwide as of 4 July 2020.¹ While most patients experience mild respiratory illness, 15% present with moderate to severe pneumonia and 5% require intensive supports for critical illness.² A recent meta-analysis demonstrated chronic kidney disease (CKD) to be associated with greater risk of severe COVID-19 infection.³

While management is largely supportive, many disease-modifying treatments such as anti-virals and immunosuppressants are in investigation, but not yet adopted into formal guidelines for treatment in Australia as per the National COVID-19 Clinical Evidence Taskforce.

Tocilizumab, a humanised anti-IL-6 antibody, has been used safely and effectively in the treatment of rheumatological conditions, as well as to deter CRS caused by chimeric antigen receptor-T cell antibody-based immunotherapy.^{4,5} The rationale for use in severe COVID-19 comes from autopsy assessments of ARDS-related lung damage in COVID-19 as well as blood samples of critically ill COVID-19 patients indicating CRS to be a major culprit.^{6,7} CRS is an excessive, unregulated

inflammatory response, with increased production of cytokines such as IL-6. Pathogenic Th1 cells and inflammatory monocytes (with high expression of IL-6) have been isolated from the peripheral blood of COVID-19 patients, and in larger numbers in critically ill patients.⁸ The most dramatic period of clinical deterioration in our patient coincided with the highest CRP, ferritin, and IL-6 levels, strongly indicating the role of CRS in her illness trajectory. Her mortality at this point would have been high, based on the findings of a retrospective, multicentre study of 150 confirmed COVID-19 cases in Wuhan, China. They showed that higher levels of ferritin (mean 1297.6 ng/mL in non-survivors vs 614.0 ng/mL in survivors; $P < .001$) and IL-6 ($P < .0001$) were associated with higher mortality.⁹ A prospective trial in Italy with 100 patients with COVID-19 needing a ventilatory support who received Tocilizumab either in ICU or on the ward (when ICU beds were to capacity), found an improvement or stabilisation in respiratory condition in 77% of patients, and worsening in 23% patients, of whom 20% died.¹⁰

COVID-19 in dialysis patients is not as well described or understood. A case series in Italy recorded a very high mortality of 41% in a haemodialysis population, compared with a mortality of 10% in non-CKD patients.¹¹ Postulated reasons for increased risk of severe COVID-19 infections in CKD patients include cardiac and other comorbidities, as well as a relative immunocompromised state.^{12,13} Perhaps CKD patients are also prone to CRS due to their chronic inflammatory state, making them more susceptible to severe disease. Severe cases in the Italian case series were treated with Hydroxychloroquine and/or antiretroviral therapies based on the discretion of an infectious diseases specialist, but none of the patients received Tocilizumab.

A haemodialysis case in the United States managed with Tocilizumab had a successful outcome, but its use coincided with the introduction of broad-spectrum antibiotics, which may have been a confounder.¹⁴ In the case of our patient, the only significant therapeutic change in the 9 hours between the peak of her CRP and the first detected fall in CRP, apart from use of nitric oxide, was the introduction of Tocilizumab.

There are case reports^{15,16} emerging of the use of continuous renal replacement therapy with extracorporeal blood purification technology to remove inflammatory cytokines such as CRP, IL-1 and IL-6, instead of the use of Tocilizumab, which is IL-6 specific. These strategies have had some reported success. Our case did not use this technique. A retrospective observational study has just completed in China, and results are awaited.¹⁷

In conclusion, we describe a case of successful recovery from CRS secondary to COVID-19 with Tocilizumab in a critically ill elderly patient on long-term haemodialysis. Tocilizumab, an IL-6 inhibitor, may be useful as a rescue therapy for CRS secondary to severe COVID-19 even in haemodialysis patients, who have severely elevated inflammatory markers including CRP and ferritin, and increasing ventilation requirements such as our case. We await current and future randomised controlled trials to shed further light on this.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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