



Tocilizumab for severe COVID-19 pneumonia: Case series of 5 Australian patients

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Abstract

Aim: To describe the first Australian cases of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2) disease (COVID-19) pneumonia treated with the interleukin-6 receptor antagonist tocilizumab.

Methods: Retrospective, open-label, real-world, uncontrolled, single-arm case series conducted in 2 tertiary hospitals in NSW, Australia and 1 tertiary hospital in Victoria, Australia. Five adult male patients aged between 46 and 74 years with type 1 respiratory failure due to COVID-19 pneumonia requiring intensive care unit (ICU) admission and biochemical evidence of systemic hyperinflammation (C-reactive protein greater than 100 mg/L; ferritin greater than 700 µg/L) were administered variable-dose tocilizumab.

Results: At between 13 and 26 days follow-up, all patients are alive and have been discharged from ICU. Two patients have been discharged home. Two patients avoided endotracheal intubation. Oxygen therapy has been ceased in three patients. Four adverse events potentially associated with tocilizumab therapy occurred in three patients: ventilator-associated pneumonia, bacteremia associated with central venous catheterization, myositis and hepatitis. All patients received broad-spectrum antibiotics, 4 received corticosteroids and 2 received both lopinavir/ritonavir and hydroxychloroquine. The time from first tocilizumab administration to improvement in ventilation, defined as a 25% reduction in fraction of inspired oxygen required to maintain peripheral oxygen saturation greater than 92%, ranged from 7 hours to 4.6 days.

Conclusions: Tocilizumab use was associated with favorable clinical outcome in our patients. We recommend tocilizumab be included in randomized controlled trials of treatment for patients with severe COVID-19 pneumonia, and be considered for compassionate use in such patients pending the results of these trials.

**KEY WORDS**

acute respiratory distress syndrome, coronavirus, immunomodulation, interleukin-6, pneumonia, tocilizumab, viral

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) on 11 March 2020. As at 24 May 2020 there have been 7135 cases of COVID-19 confirmed in Australia, of which 947 (13%) have been hospitalized, 202 (21%) required intensive care unit (ICU) admission and 102 have died.¹

Twenty percent of COVID-19 cases can develop acute respiratory distress syndrome (ARDS), which confers up to 62% mortality.^{2,3} Despite low rates of severe disease in Australia,⁴ therapies for COVID-related ARDS are urgently needed.

There is emerging evidence that COVID-19-related ARDS is triggered by excessive secretion of pro-inflammatory signaling molecules, termed cytokine release syndrome (CRS).² While there is no consensus definition of COVID-19 CRS, current data suggest it is clinically characterized by rapid-onset respiratory failure and biochemically characterized by raised interleukin-6 (IL-6) and its surrogate markers, including C-reactive protein (CRP) and ferritin.^{5,6}

Tocilizumab, a humanized monoclonal antibody targeting the IL-6 receptor (IL-6R), was approved by the Therapeutic Goods Administration for the treatment of rheumatoid arthritis in Australia in 2009.⁷ Established uses have since expanded to include juvenile idiopathic arthritis (JIA), giant cell arteritis, chimeric antigen receptor (CAR) T-cell therapy CRS and secondary hemophagocytic lymphohistiocytosis (sHLH) related to JIA, also termed macrophage activation syndrome.⁸ Although tocilizumab is generally well tolerated in patients with rheumatic diseases, serious infections are reported at a rate of 4.7 events per 100 patient-years of use, including bacterial, viral and opportunistic infections, some of which have been fatal.⁷ Tocilizumab is relatively contraindicated in patients with active infection.^{7,9}

Some clinical and laboratory findings in COVID-19 CRS are similar to those found in sHLH and CRS induced by CAR T-cell therapy.^{2,10} However, it is not yet known whether IL-6, which is implicated as causative in the latter two conditions^{2,11} plays a similar role in COVID-19 CRS.^{8,11} IL-6 is also raised in severe sepsis,¹² but data related to tocilizumab in sepsis are limited to in vitro and animal studies, and other immune interventions in sepsis using tumor necrosis factor alpha and interleukin-1 antagonists have not been associated with improved outcomes.^{13,14}

Following the publication of two small, uncontrolled, retrospective case series from China,¹⁵ there has been considerable interest in tocilizumab use in patients with COVID-19.^{2,10,16} Two case control series reporting positive short-term outcomes have now been published in the peer-reviewed scientific literature,^{17,18} and two additional case control series have been published to the preprint

server *medRxiv* but are yet to undergo peer review.^{19,20} We describe our experience using tocilizumab in patients with severe COVID-19 pneumonia.

2 | MATERIALS AND METHODS

Between 30 March 2020 and 11 April 2020, 5 patients with clinical deterioration in the context of a systemic inflammatory response to COVID-19 were treated with tocilizumab at three tertiary referral hospitals, 2 in NSW and 1 in Victoria. All patients had confirmed SARS-CoV2 infection based on real-time polymerase chain reaction analysis of nasal swab sample, radiological findings consistent with COVID-19 pneumonia and biochemical evidence of systemic inflammation with CRP greater than 100 mg/L (NR [normal range] \leq 5 mg/L) and ferritin greater than 700 μ g/L (NR 30-400 μ g/L). At the time of tocilizumab administration, three patients met the Berlin ARDS definition,²¹ had undergone endotracheal intubation and were mechanically ventilated due to type 1 respiratory failure. The other 2 patients had rapid, progressive type 1 respiratory failure but did not meet the Berlin ARDS definition as continuous positive airway pressure was not applied due to concern for aerosolization of SARS-CoV2. The decision to treat with tocilizumab was made by consensus between the involved intensive care, respiratory, infectious diseases and immunology specialists. Informed consent was obtained from the patient in two cases and from the next of kin in the three intubated patients. Clinical information for each patient was obtained from a review of electronic and paper medical record systems, from which sequential organ failure assessment (SOFA) score²² and H-score²³ were calculated where possible. Ethics approval was not required at two sites and was obtained at one site. All patients consented to publication.

3 | RESULTS

The five patients were aged between 46 and 74 years and were followed for between 13 and 26 days after tocilizumab therapy; see Figure 1. Table 1 describes patient demographics, past medical history and time-course of events prior to tocilizumab administration. All patients additionally received broad-spectrum antibiotics; four patients received corticosteroids; and two received both hydroxychloroquine and lopinavir/ritonavir (LPV/r). The time from tocilizumab administration to improvement in oxygenation, defined as a 25% fall in fraction of inspired oxygen (FiO₂) required to maintain peripheral oxygen saturation (SpO₂) greater than 92%, ranged from 7 hours to 4.6 days; Table 2 describes tocilizumab dose, additional medications administered, progress following treatment and adverse events. Table 3 and Figure 2 describe

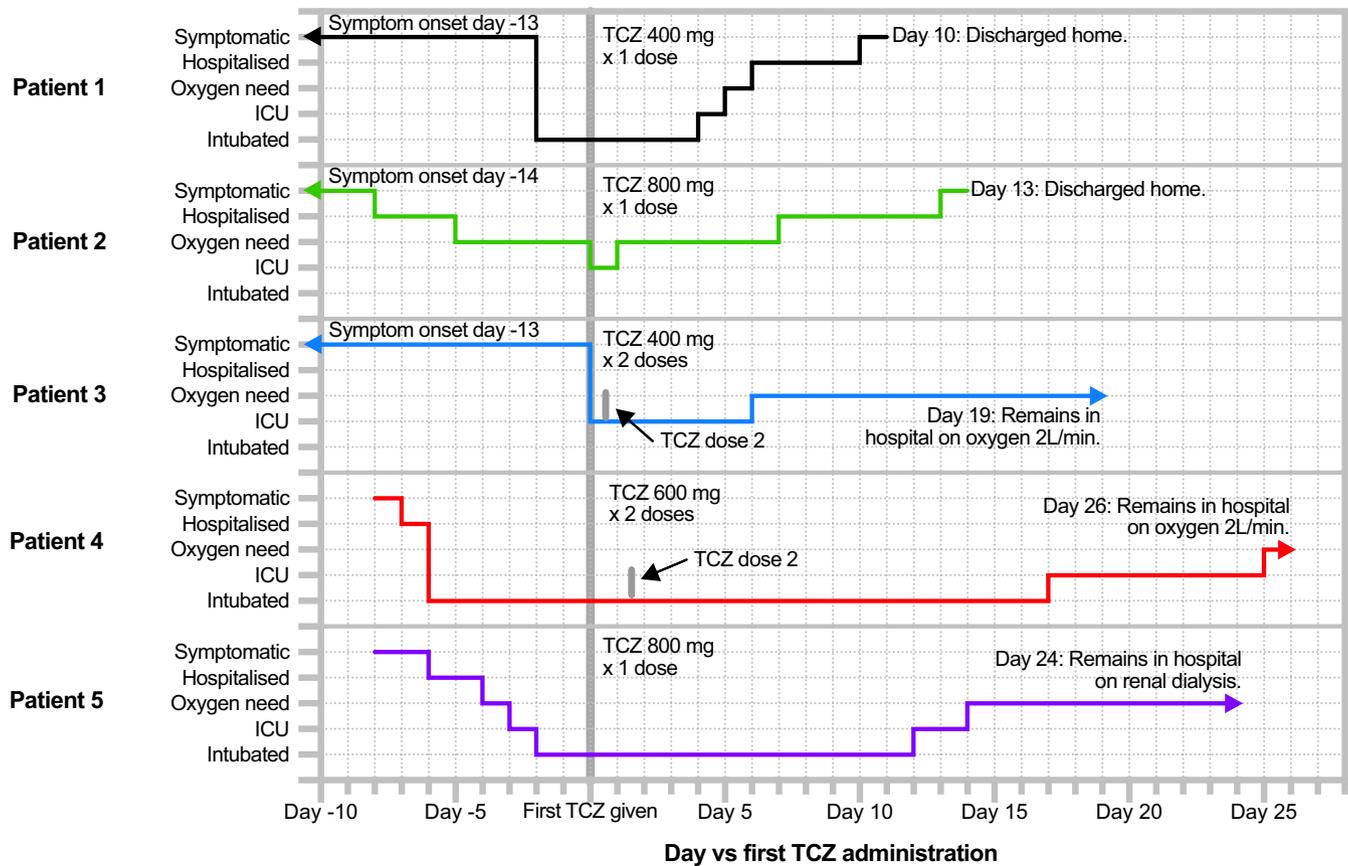


FIGURE 1 Timeline of clinical progress of COVID-19 patients before and after tocilizumab treatment. COVID-19, coronavirus disease 2019; ICU, intensive care unit; L/min, liters per minute; TCZ, tocilizumab [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

clinical and laboratory results before and after tocilizumab treatment, and in Table S1 the Supplementary Appendix details further laboratory parameters.

3.1 | Patient 1

A 53-year-old man with a history of hypertension presented to hospital with fever and rapid-onset type I respiratory failure due to COVID-19 pneumonia. At presentation, partial pressure of oxygen in arterial blood (PaO₂) was 99 mm Hg while receiving FiO₂ 80% yielding PaO₂ to FiO₂ ratio (PF ratio) of 93 mm Hg. He underwent endotracheal intubation and was mechanically ventilated using the ARDSNet protocol²⁴ to manage adequate gas exchange and noradrenaline to maintain mean arterial blood pressure greater than 70 mm Hg. A total of 6 days LPV/r and hydroxychloroquine were administered commencing at day 2 of hospitalization. On day 3 of hospitalization, intravenous (IV) tocilizumab 400 mg and methylprednisolone 70 mg (1 mg/kg) were administered. Noradrenaline was ceased 6 hours after tocilizumab administration. Two days after tocilizumab therapy, ventilatory function improved, but signs of encephalopathy arose when sedation was weaned. Corticosteroids were therefore ceased and encephalopathy resolved rapidly. Ventilator-associated pneumonia, diagnosed 3 days after tocilizumab

administration, was treated with piperacillin/tazobactam. Three days following tocilizumab administration, the patient was extubated. He was discharged from ICU 5 days after tocilizumab administration, ceased oxygen therapy 1 day later, and was discharged home after a further 4 days.

3.2 | Patient 2

A 74-year-old man with a history of type II diabetes and hypertension presented to hospital with COVID-19 pneumonia, with SpO₂ 95% on room air at presentation. He became hypoxic on admission day 3, and oxygen therapy, ceftriaxone and azithromycin were commenced. On day admission 9 he developed rapid-onset type I respiratory failure with clinical and biochemical features of COVID-19 CRS. PaO₂ was 119 mm Hg while receiving oxygen 8 L/min via Hudson mask (estimated FiO₂ 60%) yielding a PF ratio of 198 mm Hg. He was admitted to ICU and tocilizumab 800 mg IV was administered. Following tocilizumab administration, estimated FiO₂ requirement fell from 60% to 36% in 16 hours while maintaining SpO₂ greater than 92%. He did not require endotracheal intubation. He was discharged from ICU 20 hours after tocilizumab administration. He then remained stable on FiO₂ 36% for 5 days, when oral prednisone 25 mg daily was commenced. Oxygen therapy was ceased 7 days

**TABLE 1** Patient background, time-course of admission and assessment prior to tocilizumab administration

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographic data and medical background					
Age (y)	53	74	71	70	46
Gender	Male	Male	Male	Male	Male
Weight (kg)	70	90	68	72	86
BMI (kg/m ²)	25.1	27.2	23.0	26.5	32.8
Smoker	No	No	No	No	No
Ethnicity	Chinese	Caucasian	Caucasian	Indian	Filipino
Coexisting chronic diseases	Hypertension, dyslipidemia	Type II diabetes mellitus, hypertension	Dyslipidemia, aortic valve replacement, lacunar stroke	Type II diabetes mellitus	Asthma, obesity
Regular medications	Rosuvastatin, telmisartan	Allopurinol, aspirin, gliclazide MR, irbesartan, metformin, rosuvastatin	Aspirin, pantoprazole, ramipril, rosuvastatin, warfarin	Metformin	Salbutamol as-needed
Time-course from day of symptom onset					
Event	Days later	Days later	Days later	Days later	Days later
SARS-CoV2 swab + ve	2	3	1	2	0
Hospital admission	11	6	13	2	3
O ₂ requirement started	11	9	13	3	5
ICU admission	11	14	13	3	6
Intubation	11	(Not intubated)	(Not intubated)	3	7
TCZ administration	11	14	13	9	9
Assessment prior to TCZ					
PF ratio (mm Hg)	124	198	93	112	69
SOFA score	6	2	2	7	14
H-score	Insufficient data	Insufficient data	Insufficient data	151	132
Infection screen					
When tested vs TCZ	4 d prior	2 h after	3 h prior	11 h prior	Not tested
QuantIFERON Gold	Indeterminate	Indeterminate	Indeterminate	Not tested	Not tested
Hepatitis B serology	Vaccinated	Negative	Negative	Negative	Not tested
HIV serology	Negative	Negative	Negative	Negative	Not tested

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; ICU, intensive care unit; MR, modified release; O₂, oxygen; PF ratio, ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen; SARS-CoV2, severe acute respiratory syndrome-coronavirus 2; SOFA, sequential organ failure assessment; TCZ, tocilizumab.

after tocilizumab administration, and he was discharged home 6 days later. Corticosteroids were tapered to cessation over 2 weeks.

3.3 | Patient 3

A 71-year-old man with a history of bioprosthetic aortic valve replacement and lacunar stroke presented to hospital with fever and acute type I respiratory failure due to COVID-19 pneumonia. PaO₂ was 56 mm Hg while receiving oxygen 8 L/min via Hudson mask (estimated FiO₂ 60%) yielding a PF ratio of 93 mm Hg. He was immediately admitted to ICU and 2 doses of 400 mg tocilizumab were administered 8 hours apart. FiO₂ requirement reduced to 36% while

maintaining SpO₂ greater than 92% 50 hours after first tocilizumab administration. He did not require endotracheal intubation and complied with conscious proning for 16 hours per day. He received 3 days of LPV/r and 6 days of hydroxychloroquine; all were ceased due to prolonged corrected QT interval on electrocardiogram. He was discharged from ICU 6 days after tocilizumab administration. Twelve days after tocilizumab administration he developed hepatitis, which resolved over 5 days without specific intervention. A screen for infectious and autoimmune hepatitis was negative. Abdominal ultrasound demonstrated hepatic steatosis. Gastroenterology opinion was of either drug-induced liver injury or COVID-19 hepatitis. On day 19 after tocilizumab administration he remained admitted to hospital, requiring oxygen via nasal cannulae.

**TABLE 2** Tocilizumab treatment, other treatments received and response to tocilizumab administration

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
TCZ dose	400 mg IV x 1 dose	800 mg IV x 1 dose	400 mg IV x 2 doses 8 h apart	600 mg IV x 2 doses 39 h apart	800 mg x IV 1 dose
Medication	Dose and duration	Dose and duration	Dose and duration	Dose and duration	Dose and duration
Other treatments received					
Corticosteroids	MP 1 mg/kg IV daily x 2 doses from d of TCZ	P 25 mg/d tapered to cessation from 5 d after TCZ	No	P 25 mg/d x 3 d then 75 mg/d x 3 d finishing on d of hospitalization	MP 1 g x 1 dose, 100 mg/d x 3 d, 40 mg x 3 d, 5 mg x 1 d from d of TCZ
Antiretrovirals	LPV/r 400 mg/100 mg BD x 6 d from d of TCZ	No	LPV/r 400 mg/100 mg BD x 3 d from d of TCZ	No	No
Antimalarial	HCQ 200 mg BD x 6 d from d of TCZ	No	HCQ 200 mg BD x 6 d from d of TCZ	No	No
Event	Days later	Days later	Days later	Days later	Days later
Timing from d of TCZ to key clinical events					
Extubation	4	(Not intubated)	(Not intubated)	17	12
ICU discharge	5	1	6	24	14
O ₂ therapy cessation	6	7	Not yet achieved	Not yet achieved	14
Hospital discharge	10	13	Not yet achieved	Not yet achieved	Not yet achieved
Final day of follow-up	25	13	19	26	24
Criterion	Time vs TCZ	Time vs TCZ	Time vs TCZ	Time vs TCZ	Time vs TCZ
Response to TCZ administration					
Defervescence (fever < 38°C)	Immediate	3 d prior to TCZ	Immediate	Immediate	5 h
FiO ₂ fall > 25%	4.6 d	15 h	50 h	4.0 d	7 h
CRP fall > 25%	37 h	46 h	35 h	18 h	31 h
CRP fall > 50%	37 h	46 h	35 h	41 h	31 h
Ferritin fall > 25%	62 h	22 h	Not achieved	41 h	55 h
Ferritin fall > 50%	Not achieved	Not achieved	Not achieved	17.6 d	10.3 d
Radiographic improvement	41 h	9.8 d	10.2 d	7.1 d	3.3 d
Adverse events	Ventilator-associated pneumonia.	Nil.	Hepatitis.	Delirium.	Renal failure, myositis, line-associated <i>Staphylococcus epidermidis</i> bacteremia, eosinophilia.

Abbreviations: BD, twice daily; CRP, C-reactive protein; FiO₂, fraction of inspired oxygen; HCQ, hydroxychloroquine; ICU, intensive care unit; IV, intravenous; LPV/r, oral lopinavir/ritonavir; MP, intravenous methylprednisolone; O₂, oxygen; P, oral prednisolone; PO, per oral; TCZ, tocilizumab.

3.4 | Patient 4

A 70-year-old man with a history of recently diagnosed type II diabetes presented to hospital with acute type I respiratory failure due to COVID-19 pneumonia, with PF ratio of 343 mm Hg and CRP of 91 mg/L at hospital admission. Intravenous ceftriaxone and azithromycin were commenced. On day 2 of hospitalization,

he was admitted to ICU, underwent endotracheal intubation and commenced mechanical ventilation. Noradrenaline was administered to maintain mean airway pressure >70 mm Hg. By admission day 7, PF ratio was 112 mm Hg and CRP was 530 mg/L. Starting on admission day 7, 2 doses of tocilizumab 600 mg (8 mg/kg) were administered 39 hours apart and IV piperacillin/tazobactam was commenced. Following tocilizumab dose 1, he remained critically



TABLE 3 Clinical and laboratory parameters of COVID-19 patients before and after TCZ treatment

Case No.	Before TCZ therapy		Days after TCZ therapy										Clinical outcome
	Day of hospitalization	Day of ICU admission	2	3	4	5	6	7	10				
Ventilation and oxygenation													
1	Time vs TCZ	2 d prior	Same day										Discharged home d 10 post-TCZ.
	O2 delivery method	ETT	ETT	ETT	NP	NP	NP	NP	RA	RA	RA	RA	
	FiO2 (%)	80	30	30	35	36	28	21	21	21	21	21	
	PF ratio (mm Hg)	124	253	253	209	226	306	286					
2	Time vs TCZ	8 d prior	Same day										Discharged home d 13 post-TCZ.
	O2 delivery method	RA	HM	HM	NP	NP	NP	NP	NP	NP	NP	RA	
	FiO2 (%)	21	60	60	36	36	32	28	28	28	21	21	
	PF ratio (mm Hg)		198	198	277								
3	Time vs TCZ	Same day	Same day										D 19 post-TCZ: remains in hospital on ward bed on oxygen 2 L/min.
	O2 delivery method	HM	HM	HM	NP	NP	NP	NP	NP	NP	NP	NP	
	FiO2 (%)	60	60	60	36	36	36	36	36	36	36	28	
	PF ratio (mm Hg)	93	93	93	277								
4	Time vs TCZ	7 d prior	6 d prior										D 26 post-TCZ: remains in hospital on ward bed on oxygen 2 L/min.
	O2 delivery method	RA	ETT	ETT	ETT	ETT	ETT	ETT	ETT	ETT	ETT	ETT	
	FiO2 (%)	21	45	55	70	60	40	30	30	40	40	40	
	PF ratio (mm Hg)	342	112	112	81	95	165	186	186	140	140	165	
5	Time vs TCZ	6 d prior	2 d prior										D 24 post-TCZ: remains in hospital on ward bed, breathing room air, on renal dialysis.
	O2 delivery method	RA	HM	ETT	ETT	ETT	ETT	ETT	ETT	ETT	ETT	ETT	
	FiO2 (%)	RA	30	100	50	35	35	30	30	35	30	30	
	PF ratio (mm Hg)		183	69	128	314	171	213	213	200	200	267	
CRP (mg/L; NR ≤ 4.9)													
1		227	236	236	86	33	16	4	3				
2		82	128	128	37	17	12	6					
3		269	269	269	86	40	21	7				2	
4		91	226	530	389	164	40	17				12	
5		87	105	312	177	89	23	6				3	
Ferritin (µg/L; NR 30-400)													
1		4700	4396	4396	4501	2684						2670	
2		259	738	738	545	470	457	420				420	

(Continues)

TABLE 3 (Continued)

Case No.	Before TCZ therapy		Days after TCZ therapy										Clinical outcome
	Day of hospitalization	Day of ICU admission	Day of TCZ therapy	2	3	4	5	6	7	10			
3	731	731	731	774	865	812	762	681	669		546		
4			3177	2666		2296							
5			2080	2074	1611	1501							
LDH (U/L; NR ≤ 250)													
1	471	362	362	466	466	288			394				
2		255	255	213	221		227	231	202				
3	731	731	417	309	328	281	254	291	230		270		
4			324	303	303	280							
5			705			541							

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ETT, endotracheal tube; FIO₂, fraction of inspired oxygen; HM, Hudson mask; ICU, intensive care; LDH, lactate dehydrogenase; NP, nasal prongs; NR, normal range; O₂, oxygen; PF ratio, ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen; RA, room air; TCZ, tocilizumab; U/L, units per liter.

unwell for 3 days. His PF ratio improved to 185 mm Hg on day 4 following the first dose of tocilizumab and noradrenaline was ceased 1 day later. Seventeen days after tocilizumab, his PF ratio was 303 mm Hg and he was extubated. Twenty-four days after tocilizumab he was discharged from ICU, and on day 26 after tocilizumab administration he remained admitted to hospital, receiving oxygen via nasal cannulae. Fluctuating delirium has been his only complication.

3.5 | Patient 5

A 46-year-old man with a history of obesity and asthma presented to hospital with COVID-19 pneumonia, with SpO₂ 95% on room air at presentation. He developed type I respiratory failure on admission day 3 and underwent endotracheal intubation and mechanical ventilation on day 4. He developed acute kidney injury on admission day 5 requiring continuous renal replacement therapy by day 6. On day 6, PF ratio was 69 mm Hg and there were clinical and biochemical features of CRS. Manual proning was instituted, and a single dose of tocilizumab 800 mg IV and 1 g of IV methylprednisolone were administered, followed by IV methylprednisolone 100 mg daily for 3 days tapered to cessation over four further days. PF ratio improved to 193 mm Hg the day after tocilizumab administration, and he was extubated 11 days later. Oxygen therapy was ceased 15 days after tocilizumab administration.

His admission was complicated by myositis of uncertain etiology. Magnetic resonance imaging of the spine on day 17 post-tocilizumab demonstrated extensive inflammation of the left psoas and iliacus muscles and surrounding the left lumbar plexus. He further suffered *Staphylococcus epidermidis* bacteremia attributed to central venous catheterization, treated with IV vancomycin and venous catheter removal, and developed an eosinophilia (peak 1.9×10^9 cells/L) for which investigations are ongoing. At 24 days after tocilizumab administration, he remains admitted to hospital and dialysis-dependent. Renal biopsy is being considered.

4 | DISCUSSION

We present the first Australian cases of tocilizumab use in COVID-19, comprising five patients with severe COVID-19 pneumonia and clinical suspicion for CRS. Our retrospective, uncontrolled, open-label, variable protocol, real-world evidence series should be interpreted with caution. Nevertheless, we believe it is vital that such cases are published to inform current debate and to generate clinical hypotheses about mechanisms of disease and the potential for interventions.

At 13 to 26 days follow-up of our five patients, 2 had been discharged home and 3 had left ICU but remained hospitalized. Three of 5 patients had ceased oxygen therapy. Where used, corticosteroids, LPV/r and hydroxychloroquine could have contributed to these outcomes. Further, there were several adverse events, including 1 with

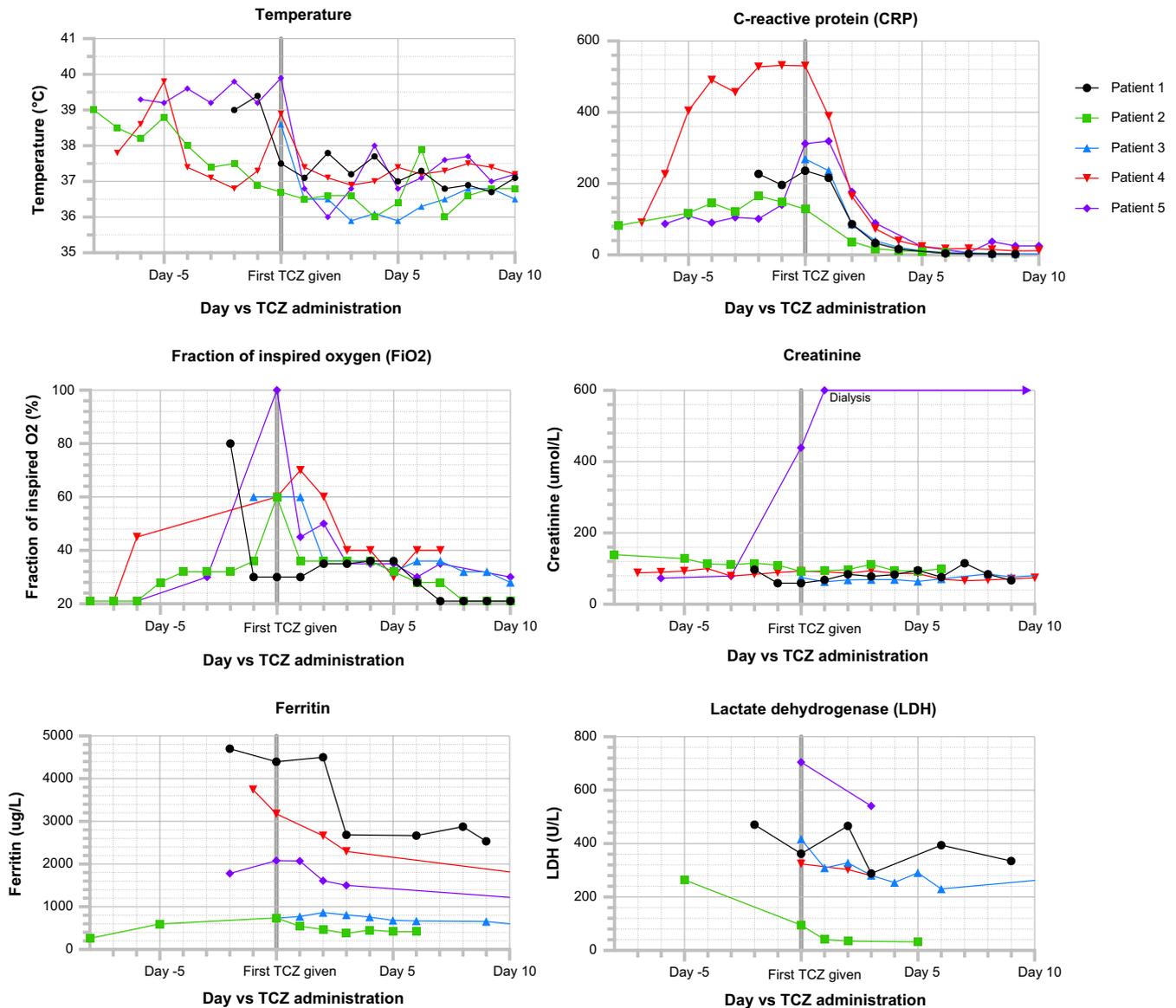


FIGURE 2 Clinical and laboratory parameters of COVID-19 patients before and after TCZ treatment. COVID-19, coronavirus disease 2019; TCZ, tocilizumab [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.com)]

patient bacterial ventilator-associated pneumonia, hepatitis, myositis and bacteremia attributed to central venous catheterization. Tocilizumab could be implicated in these events, but these findings are not uncommon in the critically ill and we await the results of randomized controlled trials to clarify the safety of tocilizumab in this population¹⁵; LPV/r could also have contributed to hepatitis.

In the face of a rapidly expanding pandemic and when evidence-based therapies or randomized trials of novel treatments are not available, it may be ethical to offer treatments with biologic plausibility and an established role in analogous diseases on a compassionate basis to patients in specific circumstances. For example, in the United States, both the Food and Drug Administration (FDA)²⁵ and American Medical Association (AMA)²⁵ state that compassionate use may be considered if:

1. There is no comparable or satisfactory therapy available,

- the probable risk from the investigational product is not greater than the probable risk from the disease, and
- providing the investigational product will not interfere with the conduct of clinical trials.

The significant mortality of severe COVID-19 pneumonia provides further justification for administration of biologically plausible but unproven treatments within these parameters; this argument was also employed during the 2014-2015 Ebola outbreak.²⁶

Of central importance is whether the inflammatory response to COVID-19 is an adaptive response to severe infection, and when, if at all, pathogenic hyperinflammation occurs. Raised levels of IL-6 have been shown to predict poor outcomes in severe COVID-19 infection, and our data add to the published literature suggesting IL-6 pathway inhibition may be beneficial.¹¹ However, IL-6 levels are also elevated in sepsis,¹² where immune interventions have failed



to show benefit.¹³ Further research into the immune response to SARS-CoV2 infection is required.

Should Level 1 evidence for tocilizumab in COVID-19 CRS emerge, patient selection and timing of drug administration will become crucial questions. Several protocols have been published, although none are backed by robust clinical data.^{27,28} Our results can be regarded only as hypothesis-generating. Physicians considering the potential value of tocilizumab in COVID-19 in absence of robust evidence should consider whether the risk of benefit outweighs the risk of harm, particularly in view of the known roles of IL-6 in host defense to viruses and the lack of a clear demarcation between adaptive and maladaptive inflammatory immune responses to infection. Treatment in mild or early infection could result in suppression of beneficial, antiviral effects of IL-6-mediated inflammation, whereas treatment too late may be ineffective.

The dose and schedule of tocilizumab used in our series varied between patients, and there is treatment heterogeneity in the published literature.¹⁵ If tocilizumab is shown to be effective for COVID-19 CRS, phase 2 dosing studies will be required. If global supply comes under strain, the needs of both COVID and non-COVID patients for tocilizumab will need to be considered.

In our series, the time from tocilizumab administration to an improvement in oxygenation, defined as a 25% fall in FiO₂ requirement, ranged from 7 hours to 4.6 days, and radiographic improvement occurred at between 41 hours and 9.8 days. While no laboratory parameter reliably predicted clinical improvement in all five patients, changes in ferritin and lactate dehydrogenase generally correlated with clinical improvement, whereas D-dimer, creatine kinase, troponin-T and neutrophil counts did not. While all patients rapidly defervesced and CRP rapidly normalized, these are IL-6-dependent processes,²⁹ and so are unlikely to predict clinical improvement.

This series illustrates that tocilizumab can be associated with favorable clinical outcome in some cases of severe COVID-19 pneumonia. The Australian Society for Clinical Immunology and Allergy (ASCIA) recommends IL-6 blockade be considered early in critically ill patients with severe COVID-19 pneumonia.⁹ We concur with these recommendations and advocate for collaborative, multidisciplinary management of such patients, including judicious use of tocilizumab, while awaiting the results of large multicenter placebo-controlled randomized trials.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

ETHICAL APPROVAL

Ethics approval was obtained from the Monash Health Human Research Ethics Committee. All patients had an opportunity to review the manuscript and consented to their cases being published.

DATA AVAILABILITY STATEMENT

All authors had full access to all of the data in the study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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