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BRIEF COMMUNICATION

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Tocilizumab therapy in 5 solid and composite tissue transplant recipients with early ARDS due to SARS-CoV-2

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There are emerging data depicting the clinical presentation of coronavirus disease 19 (COVID-19) in solid organ transplant recipients but negligible data-driven guidance on clinical management. A biphasic course has been described in some infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), beginning with a flu-like illness followed by an intense inflammatory response characterized by elevated c-reactive protein (CRP), interleukin 6 (IL-6), and acute respiratory distress syndrome (ARDS) associated with high mortality. The exuberant and possibly dysregulated immune response has prompted interest in therapeutic agents that target the cytokines involved, particularly IL-6. Tocilizumab is an IL-6 receptor antagonist with a record of use for a variety of rheumatologic conditions and cytokine release syndrome due to chimeric antigen receptor T-cell therapy but experience in solid organ and composite tissue transplant recipients (SOT/CTTRs) with SARS-CoV-2-related ARDS has not been previously reported in detail. We present the clinical course of 5 SOT/CTTRs with SARS-CoV-2-related ARDS that received tocilizumab with favorable short-term outcomes in 4. Responses were characterized by reductions in CRP, discontinuation of vasopressors, improved oxygenation and respiratory mechanics, and variable duration of ventilator support. Four bacterial infections occurred within 2 weeks of tocilizumab administration. We discuss safety concerns and the need for randomized comparative trials to delineate tocilizumab's clinical utility in this population.

KEYWORDS

clinical research/practice, infection and infectious agents - viral, infectious disease, off-label drug use

Abbreviations: ALC, absolute lymphocyte count; ALT, alanine transaminase; ARDS, acute respiratory distress syndrome; AST, aspartate transaminase; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CRS, cytokine release syndrome; CXR, chest x-ray; HCQ, hydroxychloroquine; ICU, intensive care unit; IL-6, interleukin 6; LDH, lactate dehydrogenase; MDR, multidrug-resistant; MMF, mycophenolate mofetil; MV, mechanical ventilation; NP, nasopharyngeal; PaO_2/FiO_2 ratio, Partial pressure of arterial oxygen/fraction of inspired oxygen ratio; PEEP, positive end-expiratory pressure; pro-BNP, pro-B-type natriuretic peptide; RA, room air; RSV, respiratory syncytial virus; RT-PCR, real time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOT/CTTRs, solid organ and composite tissue transplant recipients; SpO_2, oxygen saturation; VAP, ventilator-associated pneumonia; XDR, extensively drug-resistant.

1 | INTRODUCTION

The novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), the causal agent of coronavirus disease 2019 (COVID-19), was first reported in Wuhan, China in December 2019,[1] and has spread rapidly to cause the worst pandemic since 1918. More than 9 million cases have been reported worldwide with mortality of 5.1% (coronavirus.jhu.edu). The poorest outcomes are described in individuals with comorbidities, including older age, diabetes, hypertension, renal failure, obesity, advanced heart, and lung disease.[2-5]

Solid organ and composite tissue transplant recipients (SOT/CTTRs) may be at greater risk for severe manifestations of infection with SARS-CoV-2 as they are for other RNA respiratory viruses, including influenza and RSV.[6] Early data from Italy, in a cohort of pediatric transplant patients, indicated that liver transplant recipients did not develop severe pulmonary manifestations, suggesting that transplant-related immunocompromise in the absence of comorbidities is not a predictor of poorer outcomes.[7] However, more recent data indicate adult SOTRs are not protected from severe manifestations of COVID-19.[8] Some have posited that transplant immune suppression may dampen the harmful immune response, making it unclear how to manage immune suppression in the setting of SARS-CoV-2 infection.

A biphasic disease course has been described in about one-third of patients with COVID-19, beginning with a flu-like illness and transitioning 7-14 days later to a period of robust immunologic response characterized by acute respiratory distress syndrome (ARDS) and elevated markers of inflammation.[9-13] The critical illness and high mortality engendered in the inflammatory phase has sparked great interest in specific cytokines, particularly interleukin 6 (IL-6), as therapeutic targets.[14]

Tocilizumab is a human monoclonal IL-6 receptor antagonist that has been used successfully for treatment of rheumatoid arthritis, giant cell arteritis, and cytokine release syndrome (CRS) due to Chimeric antigen receptor T cell therapy.[14,15] Potential side effects include liver injury and fungal, bacterial, and mycobacterial infections. Tocilizumab has now been reported as therapy in short case series of patients with severe COVID-19 and demonstrates some promise in abrogating the immediate deleterious effects of the immune response.[16] With immunologic effects that may persist for weeks, it is unclear if tocilizumab will benefit SOT/CTTRs in the setting of existing immune suppression and if there will be unanticipated consequences.

Here we present five SOT/CTTRs (Table 1) with SARS-CoV-2-related ARDS in which tocilizumab was used with favorable short-term outcomes in four. Figure 1 depicts the clinical courses of these five patients from symptom onset.

1.1 | Case 1

A 53-year-old female medical receptionist with hypertension, kyphoscoliosis, and five prior kidney transplants (latest, 5 years previously, with creatinine 1.4 mg/dL), maintained on mycophenolate mofetil (MMF), tacrolimus, and prednisone presented to the emergency room (ER) with cough, chest pain, fever, fatigue, diarrhea, and shortness of breath (SOB) for 4 days. Her temperature was 37.9°C, blood pressure (BP) 93/63 mm Hg, heart rate (HR) 85 beats per minute (bpm), respiratory rate (RR) 22 breaths per minute (Bpm), and oxygen saturation (SpO_2) of 92% on room air (RA). Lungs were clear to auscultation. Laboratory data showed a white blood cell count (WBC) of 8.46 k/μL (normal: 3.7-11), absolute lymphocyte count (ALC) of 0.28 k/μL (normal: 1.0-4.0), hemoglobin (Hb) of 14.3 g/dL, platelets of 127 k/μL, creatinine 1.7 mg/dL,alanine transaminase (ALT) 26 U/L, aspartate transaminase (AST) 25 U/L, lactate 1.2 mmol/L (normal 0.5-2.2). A chest x-ray (CXR) showed severe scoliosis and no pulmonary infiltrates. A nasopharyngeal (NP) swab for influenza and respiratory syncytial virus (RSV) polymerase chain reaction (PCR) was negative. SARS-CoV-2 RT-PCR was positive.

MMF was discontinued and tacrolimus dose was adjusted. The following day, she became hypotensive and more hypoxic. A CXR showed bilateral pulmonary patchy infiltrates. She was transferred to the intensive care unit (ICU) and treated with stress dose steroids, hydroxychloroquine, and lopinavir/ritonavir. Due to hypoxemia and respiratory distress, she required intubation and mechanical ventilation (day 7). Labs included ALC 0.22 k/μL, C-reactive protein (CRP) 9.7 mg/dL (ref < 0.9 mg/dL), ferritin 535 ng/mL (14.7-205.1 ng/mL), procalcitonin 0.1 ng/mL (ref < 0.09 ng/mL, and so on), lactate dehydrogenase (LDH) 234 U/L (135-214), pro-BNP 3214 (ref < 125), and troponin T < 0.010 ng/mL. Partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio was 196 (positive end-expiratory pressure [PEEP] 12 cm H_2O). Shortly after intubation, a blood sample for IL-6 concentration was collected and one dose of tocilizumab 400 mg intravenously was given. One day later, her CRP level declined to 3.5 mg/dL and continued trending down over the next days. Vasopressors and stress-dose steroids were discontinued, and ventilator settings were lowered (FiO_2 from 80% to 30%; PEEP from 12 to 5 cm H_20) over the next 3 days. On day 11 of illness, she developed fever and was found to have ventilator-associated pneumonia (VAP) due to multidrug-resistant (MDR) *Pseudomonas aeruginosa* treated with ceftolozane/tazobactam for 7 days. Pretocilizumab IL-6 level came back at 7 pg/mL (ref ≤5). She was extubated 13 days after tocilizumab dose and transferred to a regular nursing floor, where she was treated for moderately severe *Clostridioides difficile* colitis. Twenty-three days from illness onset her SARS-CoV-2 PCR testing results were negative twice separated by 24 hours. She remained hypoxic with cough and was discharged home on supplemental oxygen at 3 L/min.

1.2 | Case 2

A 78-year-old man with a history of pulmonary fibrosis with left single lung transplant (6 years previously) complicated by chronic lung allograft dysfunction requiring supplemental oxygen at 1 L/min on tacrolimus and prednisone, diabetes mellitus, heart failure, hypertension, end-stage renal disease on hemodialysis, and recent bladder cancer presented to the emergency department with dry cough and worsening dyspnea on exertion for 3 days. He was afebrile, BP 124/68 mm Hg, HR of 99 bpm,

TABLE 1 Comparison of clinical features in our solid organ transplant recipients with COVID-19 treated with tocilizumab

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)/gender	53/F	78/M	51/M	69/F	57/F
Type of transplant	KT	Single LT	Face	LiT	KT
Years after transplant	5	6	5	3	6
Immunosuppression	MMF, tacrolimus, prednisone (5 mg)	Tacrolimus, prednisone (5 mg)	Tacrolimus, prednisone (5 mg)	Cyclosporine	Azathioprine, tacrolimus, prednisone (5 mg)
Symptoms	Fever, cough, malaise, diarrhea, dyspnea	Cough, dyspnea, hypoxia	Fever, dyspnea	Fever, fatigue, myalgias, sore throat, cough, dyspnea, diarrhea	Fever, fatigue, sore throat, cough, diarrhea
Onset of symptoms to hospital admission/MV (days)	5/7	4/5	8 (outside hospital ICU)/8	6/13	4/11
Tocilizumab administration after symptoms onset/MV (days)	7/0	5/0	10/2	13/0	12/1
Other therapies	Lopinavir/ritonavir[a], HCQ[b]	HCQ[b]	HCQ[b]	HCQ[b]	HCQ[b]
Days on MV	13	4	25[+]	24	3
Peak CRP (mg/dL)	9.7	18.8	36.5	5.3	32.7
Nadir ALC (k/μL)	0.11	1.78	1.22	0.13	0.16
IL-6 (pg/mL)	7	13	438	NA	NA
Procalcitonin at time of tocilizumab administration (ng/mL)	0.10	1.07	3.12	0.11	NA
Co-infection posttocilizumab	MDR *Pseudomonas aeruginosa* pneumonia VAP/CDI	None	XDR *P aeruginosa* and *Corynebacterium striatum* VAP	Suspected bacterial superinfection, never proven	None
Outcome	Discharged	Discharged	Discharged - [+]Remains on MV	Died	Discharged

Abbreviations: ALC, absolute lymphocyte count; CDI, *Clostridioides difficile* infection; CRP, C-reactive protein; HCQ, hydroxychloroquine; IL-6, interleukin-6; KT, kidney transplant; LiT, liver transplant; LT, lung transplant; MDR, multidrug-resistant; MMF, mycophenolate mofetil; MV, mechanical ventilation; VAP, ventilator-associated pneumonia; XDR, extensively drug-resistant.

[a]Lopinavir/ritonavir: 400 mg twice daily for 7 days.

[b]Hydroxychloroquine: 400 mg every 12 h twice, followed by 200 mg every 12 h for 5 days.

RR of 32 Bpm, and SpO_2 of 91% on supplemental oxygen at 4 L/min. He had bilateral crackles on lung auscultation. Laboratory data showed WBC 17.14 k/μL, ALC 3.12 k/μL, Hb 13.1 g/dL, platelets 145 k/μL, creatinine 3.34 mg/dL, ALT 20 U/L, AST 43 U/L, lactate 1.5 mmol/L. A CXR showed a consolidative infiltrate in the left transplanted lung and stable interstitial infiltrates in the right native lung. A NP swab for rapid influenza and RSV PCR resulted negative.

He received empiric vancomycin, piperacillin-tazobactam, and azithromycin, and was admitted to the ICU where he required intubation and mechanical ventilation (day 5). NP swab for SARS-CoV-2 RT-PCR returned positive. PaO_2/FiO_2 ratio 200 (PEEP 12 cm H_2O). Laboratory findings included CRP 18.8 mg/dL, ferritin 610 ng/mL, procalcitonin 1.07 ng/mL, pro-BNP 49,000, and troponin T 0.366 ng/mL with an electrocardiogram revealing ventricular-paced rhythm. He received piperacillin-tazobactam for 5 days due to concerns for bacterial co-infection and hydroxychloroquine. A blood sample for IL-6 concentration was collected (later resulting at 13 pg/mL) and tocilizumab 400 mg intravenously was given (day 5). His CRP declined to 12.9 mg/dL 1 day later. He was extubated 4 days later and transferred to a regular nursing floor. CRP normalized after 11 days. Repeat CXR on day 17 showed improvement of left consolidation. He returned to his baseline use of supplemental oxygen (1 L/min) on day 18. His discharge was delayed due to persisting positive results of SARS-CoV-2 RT-PCR from NP swab at day 32 from symptom onset.

1.3 | Case 3

A 51-year-old man residing in a long-term care facility with morbid obesity, hypertension, diabetes mellitus, granulomatosis with

FIGURE 1. Disease course and interval events

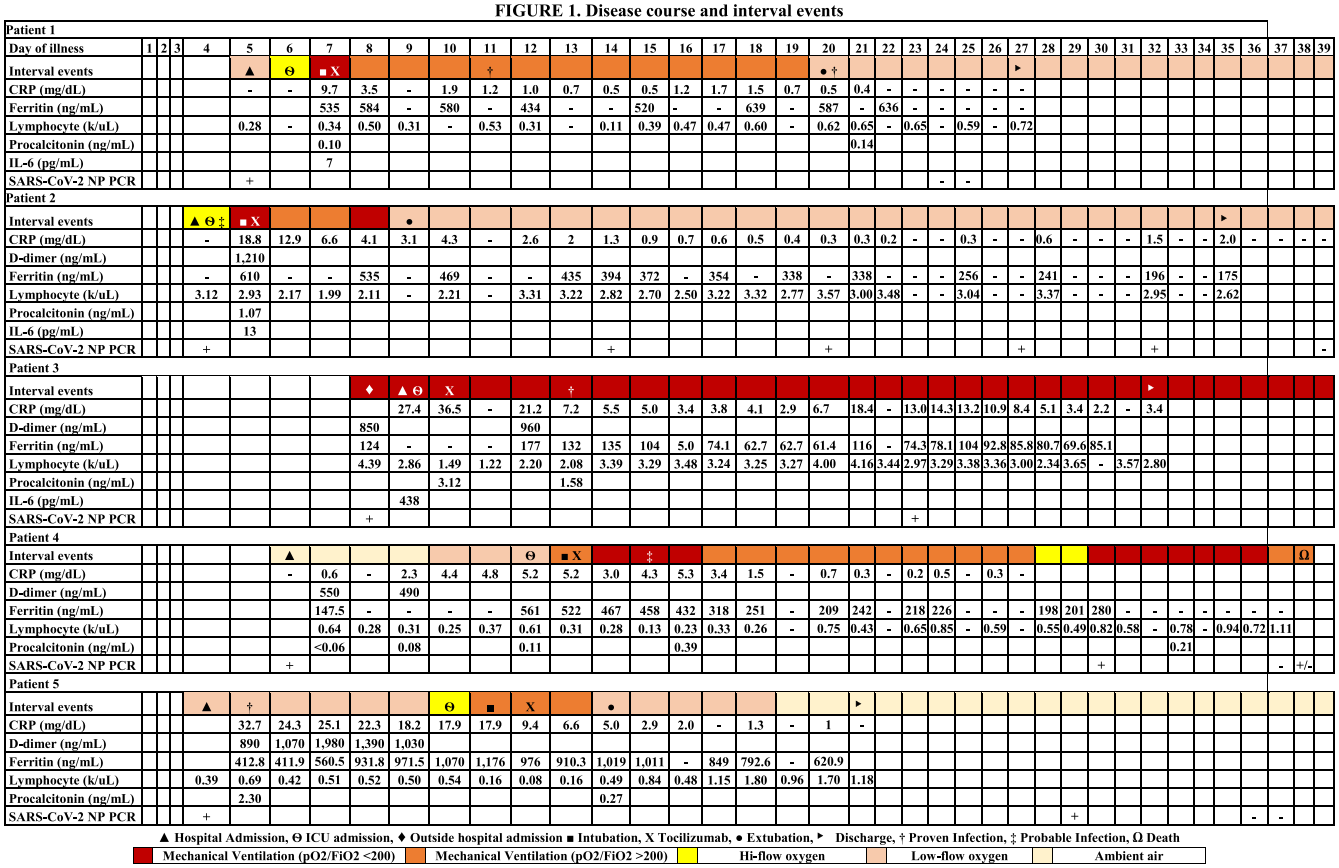

FIGURE 1 Disease course and interval events [Color figure can be viewed at wileyonlinelibrary.com]

polyangiitis in remission, face transplantation (5 years previously) due to disfigurement from a motor vehicle accident on tacrolimus and prednisone, and chronic respiratory failure (secondary to *P. aeruginosa* pneumonia) on supplemental O_2 via tracheostomy was transferred from an outside hospital ICU after 1 week of respiratory symptoms, fever, and worsening respiratory failure requiring mechanical ventilation. He was in shock requiring vasopressor support. He had a positive SARS-CoV-2 RT-PCR. His temperature was 37.9°C, BP 115/43 mm Hg on norepinephrine, HR 101 bpm, and PaO_2/FiO_2 ratio 113 (PEEP 20 cm H_2O). Lungs were clear. Laboratory data showed WBC of 19.08 k/μL, ALC 4.39 k/μL, absolute neutrophil count 13.93 k/μL, Hb 8.8 g/dL, platelets 258 k/μL, creatinine 3.94 mg/dL, ALT 47 U/L, AST 44 U/L, CRP 27.4 mg/dL, ferritin 124.0 ng/mL. Outside hospital tracheal aspirate demonstrated *P. aeruginosa*. A CXR showed possible mid-right lung and bibasilar atelectasis.

Hydroxychloroquine had been started at an outside hospital and was continued. Stress-dose steroids and empiric antimicrobials (piperacillin-tazobactam and vancomycin) were started. Laboratory data showed procalcitonin 3.12 ng/mL and CRP 36.5 mg/dL. Due to acute worsening of ventilator requirements, a blood sample for IL-6 concentration was collected (later resulting at 438 pg/mL) and one dose of tocilizumab 400 mg intravenously (day 10) was given. One day after tocilizumab, vasopressors were stopped, ventilator settings decreased, and CRP declined to 21.2 mg/dL *P. aeruginosa* was identified as susceptible and monotherapy with piperacillin-tazobactam was continued. CRP downtrended; however, he had worsening leukocytosis, hypotension, and increased respiratory secretions with worse oxygen requirement. New tracheal aspirate culture grew extensively drug-resistant (XDR) *P. aeruginosa* and started on ceftolozane-tazobactam for right-sided pneumonia. Due to persisting signs of infection, a bronchoalveolar lavage was performed and grew abundant *Corynebacterium striatum* and XDR *P. aeruginosa*. With combination therapy (ceftolozane-tazobactam, inhaled colistin, vancomycin) he improved and requiring minimal ventilatory support. He was discharged on day 24 of admission to his long-term care facility where he continues to recover.

1.4 | Case 4

A 69-year-old woman with hepatitis C liver cirrhosis resulting in liver transplant (3 years previously), who was on cyclosporine and had rheumatic heart disease and chronic kidney disease stage 3, presented to the ER with fever, fatigue, myalgias, sore throat, diarrhea, and progressive dyspnea for 6 days. Her temperature was 38.7°C, BP 124/48 mm Hg, HR 56 bpm, RR 13 Bpm, and SpO_2 98% on RA. Left-sided rales were present in the mid-lung field. Laboratory data showed WBC of 1.53 k/μL, ALC 0.47 k/μL, Hb 9.2 g/dL, platelets 76 k/μL, creatinine 1.64 mg/dL, ALT 16 U/L, and AST 30 U/L. A CXR

showed a left perihilar infiltrate. Result of an NP swab for rapid influenza and RSV PCR was negative. Empiric ceftriaxone and azithromycin were started; SARS-CoV-2 RT-PCR from NP swab was positive.

Antibiotics were discontinued. Over the next few days she developed fever, mild respiratory distress, and hypoxemia. CXR showed progressive extensive bilateral opacities. Hydroxychloroquine and supplemental oxygen via nasal cannula were started, and she was transferred to the ICU. Labs included ALC 0.31 k/μL, CRP 5.2 mg/dL, and ferritin 561 ng/mL. After a few hours, she required intubation and mechanical ventilation (day 13). PaO_2/FiO_2 ratio was 283 (PEEP 14 cm H_2O). Tocilizumab 310 mg (adjusted based on weight) intravenously was given however, baseline IL-6 level was not measured. Despite initial rapid decline in CRP, she developed new fevers and hypotension requiring vasopressors and stress-dose steroids. Repeated workup showed WBC 11.33 k/μL, CRP 5.3, and procalcitonin 0.39. CXR showed worsening consolidative opacities. Due to concern for superimposed bacterial infection, she was treated empirically with vancomycin and piperacillin-tazobactam. Fevers resolved after 2 days of antibiotics. Over the next few days, vasopressor requirements decreased, stress-dose hydrocortisone discontinued, ventilator settings were lowered, and CRP normalized. Blood and respiratory cultures were negative for infection. Unfortunately, she could not be extubated in the setting of persistent delirium, atrial fibrillation with rapid ventricular response, worsening pulmonary edema, and hemoptysis in the setting of anticoagulation. She was transitioned to comfort measures and died 2 days later.

1.5 | Case 5

A 57-year-old woman with a history of hypertension, diabetes mellitus, pulmonary embolism, coronary artery bypass graft surgery, and kidney transplantation (6 years previously) on azathioprine, tacrolimus, and prednisone presented to the ER with fatigue, sore throat, fevers, cough, and diarrhea for 4 days. Her temperature was 36.7°C, BP 134/106 mm Hg, HR 80 bpm, RR 24 Bpm, and SpO_2 91% on RA, with improvement on 2 L/min oxygen via nasal cannula. Lungs were clear. Laboratory data showed WBC of 9.72 k/μL, ALC 0.39 k/μL, Hb 12.2 g/dL, platelets 103 K/μL, creatinine 2.31 mg/dL (from prior 1.75 mg/dL), ALT 11 U/L, and AST 37 U/L. CXR showed linear densities in the right lower lung. An NP swab for influenza/RSV PCR was negative. NP swab for SARS-CoV-2 RT-PCR returned positive.

Her laboratory results were significant for a of CRP 32.7 mg/dL and a procalcitonin of 2.30 ng/mL. Hydroxychloroquine was given and azathioprine was discontinued. Empiric ceftriaxone and azithromycin were added for possible bacterial infection, which were later changed to ertapenem for extended-spectrum beta-lactamase *Escherichia coli* in urine. She had worsening respiratory status (5-6 L/min via NC) and bilateral opacities in CXR. She was transferred to the ICU and required mechanical ventilation (day 11). Labs included ALC 0.16 k/μL, CRP 17.9 mg/dL, and ferritin 1176 ng/mL. PaO_2/FiO_2 ratio was 156 (PEEP of 14 cm H_2O). She developed shock requiring vasopressors and stress-dose steroids; and acute renal failure with renal replacement therapy. Despite initial CRP decline (9.4 mg/dL), tocilizumab 400 mg intravenously was given (day 12). One day postdose the CRP declined to 6.6 mg/d, vasopressors and stress-dose steroids were discontinued, and 2 days postdose she was extubated. CRP normalized 8 days later. She was transferred to regular nursing floor and discharged on room air to a rehabilitation facility.

2 | DISCUSSION

Herein, we describe the first detailed case series of 5 SARS-CoV-2-positive SOTRs (2 kidney, 1 liver, 1 lung, and a face recipient); patients had multiple comorbidities and were critically ill, required mechanical ventilation, and were treated with a single dose of IL-6R antagonist tocilizumab early after intubation. Rapid improvements were observed in markers of inflammation and, although four of the five survived their severe illness, it is not clear how the drug affected specific facets of their clinical course.

In these patients, we observed the biphasic disease course reported previously for those developing severe COVID-19 with a mean time of 8.8 days from self-reported symptom onset to respiratory failure associated with markers of inflammation. This demonstrates that the SOT population is not protected from the inflammatory storm by their immunosuppressive drugs. However, these patients presented 3-6 years posttransplant and were not in the peak period of immunosuppression. Baseline posttransplant immunosuppression has not been associated with COVID-19 severity in 90 SOTRs described by Pereira et al.[8] Whether deliberate reduction of immunosuppression is helpful or harmful is unclear. Immunosuppression was managed in agreement with our organ transplant teams and, similar to the approach with other serious infections, consisted of stopping the antiproliferative agents, adjusting calcineurin inhibitor to a target trough 5-8 ng/mL, and increasing corticosteroids only if other indications (ie, refractory shock, COPD exacerbation, and so on) are present.

In the absence of directive data, there is uncertainty as to the dose selection, timing, and number of doses of tocilizumab for managing COVID-19-related inflammation. Some propose administration prior to ventilatory support and some propose later use once classic findings of CRS emerge.[17] Early reports from China and a recent case report of tocilizumab use in a kidney transplant recipient with COVID-19 suggested some benefit to earlier dosing.[14,16,17] With multidisciplinary input, our institution stewarded the limited tocilizumab supply by administering a single dose (capped at 400 mg) after intubation but prior to advanced multisystem organ involvement. Therefore, our patients uniformly received tocilizumab within 48 hours of mechanical ventilation, and all but one within 24 hours. Patient 3 had the most advanced signs of CRS (with very high CRP and IL-6 concentrations) at tocilizumab dosing with reversible renal failure requiring hemodialysis, although with concern for concomitant septicemia.

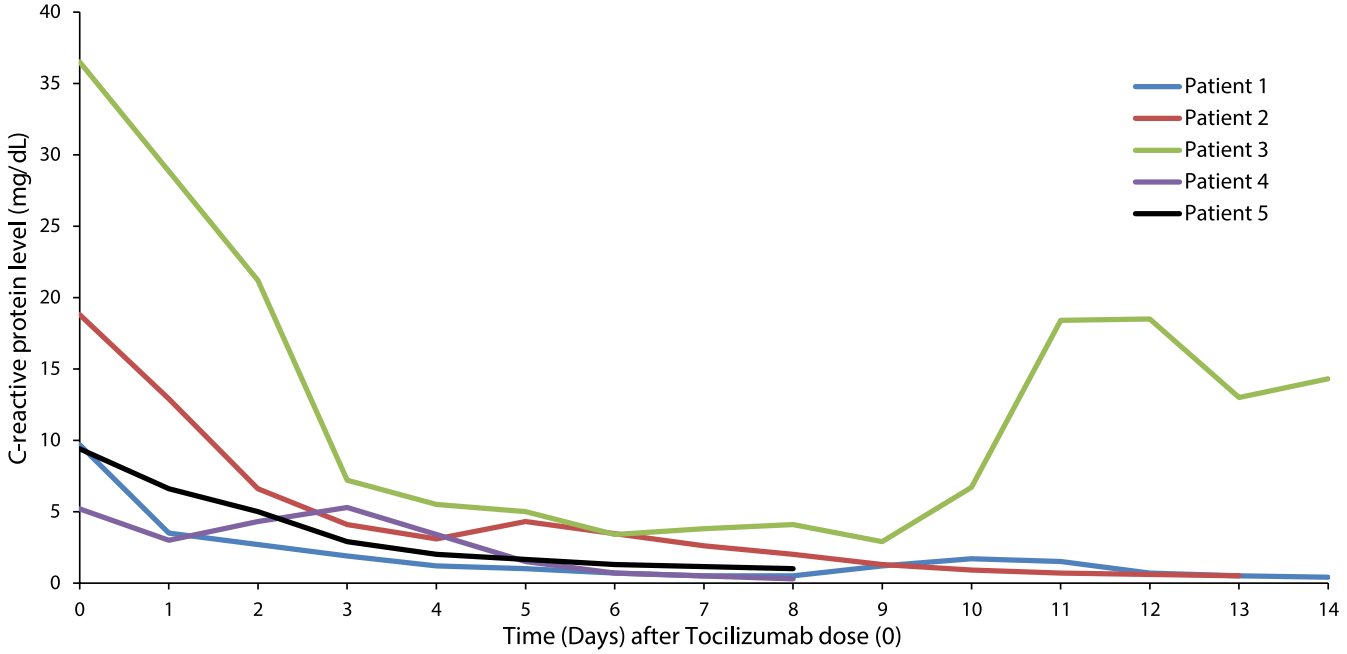

FIGURE 2 C-reactive protein (CRP) kinetics posttocilizumab injection [Color figure can be viewed at wileyonlinelibrary.com]

As expected, tocilizumab resulted in declining CRP (Figure 2) for all patients over 3-5 days.[16] Lack of normalization appeared to be associated with bacterial superinfection in patient 3. We did not have IL-6 concentrations for all patients before tocilizumab due to the 4- to 7-day turn-around time, making it less clinically directive. The predose IL-6 concentrations available for 3 patients were widely different. Although 2 patients had relatively low IL-6 levels, they fell within the range observed previously for patients with fatal outcomes.[2] Prior studies demonstrated that IL-6 can remain stable for 2 weeks, likely due to removal mechanisms (binding of receptors), and peaks on days 15-20.[11] For this reason, a surrogate of endogenous IL-6 production such as CRP may be more useful. In addition, tocilizumab blocks binding of IL-6, resulting in higher postdose detectable levels in blood. Thus, pre- and postdose IL-6 concentrations will be important in clinical trials of tocilizumab.[18]

The effects of tocilizumab on other outcomes in our patients is less certain. Four of 5 patients survived (80%) compared to 67% of those COVID-19 SOTRs requiring mechanical ventilation who did not receive tocilizumab in our regional hospital system. This may be better than in those historically reported in case series for critical COVID-19 and in 14 patients receiving tocilizumab within a recent broader series of SOTRs in New York City,[8] but our numbers are limited. For all 5 patients, measures of ventilatory support and need for vasopressors temporally improved after tocilizumab. Although 2 patients were expediently liberated from ventilatory support, the others required support for 2 or more weeks and one died awaiting tracheostomy. One patient required new supplemental O_2 at the time of discharge. Long-term impact on pulmonary function (particularly in lung transplant recipients) will remain of interest in all COVID survivors with pulmonary involvement and in those with tocilizumab therapy in particular.

It is notable that there were no immediate drug-related side effects (transaminitis, leukopenia, or thrombocytopenia), although 2 patients developed 3 proven bacterial infections within 2 weeks after dosing. One episode of MDR *P. aeruginosa* VAP (de novo infection), 1 episode of *C. difficile* infection, and one episode of XDR *P. aeruginosa/C. striatum* VAP. Although concerning, it is difficult to separate these from the risk for nosocomial infection in this patient population making additional antimicrobial prophylaxis unwarranted. Given the duration of action, longer-term impact in infection requires close follow-up. Tocilizumab offers some protection from rejection, raising the question of whether further reductions of standard immunosuppressives are merited to prevent infection and calcineurin inhibitor toxicities.[19] In addition, the impact of tocilizumab on SARS-CoV2 viral shedding requires particular attention, as 4 of 5 patients had detectable RNA beyond day 22 of illness.

In summary, we showed that tocilizumab can be used without major direct toxicity in SOT/CTTRs early after initiation of mechanical ventilation due to COVID-19, regardless of type of organ transplanted. Although it was temporally associated with the expected reductions in inflammatory markers and initial (but not always consistent) improvements in respiratory status, it is unclear whether it had any effect on major patient outcomes and if long-term side effects will transpire. Four of 5 patients survived; however, early nosocomial bacterial infections raise concerns for associated bacterial infection risk. Randomized clinical trials with comparative data are paramount to determine the true efficacy and risk of tocilizumab for use in patients, including SOT/CTTRs, with COVID-19.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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