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Case Report Open Access

SUCCESSFUL TREATMENT OF SEVERE COVID-19 IN A KIDNEY TRANSPLANT RECIPIENT WITH TOCILIZUMAB

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ABSTRACT

We report a case of severe COVID-19 in a deceased donor kidney transplant recipient (KTR) who was successfully treated with Tocilizumab. She presented with COVID-19 symptoms and tested positive by reverse transcription real-time polymerase chain reaction (RT-PCR) of nasopharyngeal swab. The patient was admitted on day 5 of illness with chest radiography (CXR) suggestive of bronchopneumonia. Blood investigations showed leucocytosis with normal lymphocyte count and raised C-reactive protein (CRP). We closely monitored her condition as she was able to maintain saturation under room air. She deteriorated further on day 9 of illness, requiring withholding of immunosuppressive medications, increasing dose of oxygen therapy and dexamethasone. Tocilizumab was started for lymphopenia, raised lactate dehydrogenase (LDH) and persistence of alveolar opacities. Complications include acute kidney injury (AKI) and transaminitis. Her symptoms of pneumonia gradually improved, was able to be discharged on day 20 of illness, with complete resolution of AKI.

Keywords: *COVID-19, Kidney Transplant, Tocilizumab*

TITLE

A case of successful treatment of severe COVID-19 in kidney transplant recipient with Tocilizumab, an interleukin-6 receptor monoclonal antibody.

INTRODUCTION

The World Health Organization declared the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak a pandemic on 11th March 2020. Coronavirus disease (COVID-19) pneumonia in kidney transplant recipients (KTR) represents a new challenge for nephrologists as they are considered a high-risk population for severe infection. COVID-19 is transmitted via droplets or direct contact and infects the respiratory tract resulting in pneumonia in most cases and acute respiratory distress syndrome (ARDS). ARDS in COVID-19 infection is related to a "cytokine storm" (CS) with large interleukin-6 (IL-6) release. Tocilizumab is a humanized antibody against the receptor of IL-6. In the setting of transplantation, Tocilizumab has been used to treat chronic antibody-mediated rejection. (1) Since ARDS in severe COVID-19 is an inflammatory response, Tocilizumab appears as a reasonable drug to target the presumed CS triggered by the virus. Thus, we share our experience with a successful KT recipient with severe COVID-19 infection treated with Tocilizumab.

CASE

A 40 years old woman who is a deceased donor KTR performed on 2nd July 2019, with stable graft function on maintenance immunosuppressive treatment of Everolimus 0.75mg BD, Prednisolone 10mg OD and Tacrolimus 2mg OD. Her baseline serum creatinine was 188µmol/L, 4 months before the COVID-19 infection. She has completed 2 doses of COVID-19 vaccination (Pfizer) on 15th July 2021. The primary renal disease was unknown.

On 19th October 2021, she experienced the onset of sore throat, cough, ageusia, anosmia, headache, and rhinorrhoea. COVID-19 recent infection was confirmed by reverse

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transcription real-time polymerase chain reaction (RT-PCR) with CT value of RDPR=27.32; N-NA; E=25.79. Therefore, she was admitted to the COVID isolation ward on 23rd October 2021.

She admitted on day 5 of illness (23rd October 2021), her vital signs were: afebrile, blood pressure 145/92mmHg, and heart rate of 120beats/minute, respiratory rate of 20breaths/minute, oxygen saturation of 96% under room air. Chest radiography (CXR) showed bilateral lower zone multifocal alveolar opacities suggestive of bronchopneumonia. Laboratory tests showed raised white cell count (WBC) 12.7X10^9 /L without lymphopenia, C-reactive protein (CRP) 250.1mg/L, and ferritin 157.20µg/L. On day 6 of illness, she had new onset of fever with a temperature of 37.8°C. IV Piperacillin-tazobactam 2.25g three times a day was initiated after blood culture and urine culture were obtained. On day 7 of illness, she developed exertional hypoxia (saturation dropped from 95% to 92%). We started oxygen supplementation through a nasal prong (3 L/min) and administered IV Dexamethasone 8mg daily.

On day 9 of illness, patient's saturation dropped further and required a venturi mask of 60% to maintain oxygen saturation >95%. Laboratory tests showed an increased in WBC to 17.1X10^9/L, neutrophil-lymphocyte ratio (NLR)=18, with lymphopenia = 0.9X10^9/L and lactate dehydrogenase (LDH) = 527U/L. She developed non-oliguric AKI (serum creatinine raised from 244µmol/L to 291µmol/L) and transaminitis (alanine transferase from 75U/L to 92U/L and aspartate aminotransferase from 37U/L to 148U/L). (Table 1). Repeated CXR remained unchanged, we commenced Tocilizumab 400mg and increased IV Dexamethasone to 24mg daily. Her immunosuppression therapies were discontinued as her creatinine and Tacrolimus drug level were rising (Tacrolimus drug level : 4.31ng/ml to 5.97ng/ml).

IV Meropenem 500mg BD was started due to rising WBC and rising NLR.

RESULTS

Three days following the initiation of Tocilizumab, her clinical condition improved with reducing CRP (42mg/L) and LDH (455U/L); CXR showing partial resolution. The patient was discharged after 2 weeks with serum creatinine returned to baseline (165 µmol/L).

Her transplant clinic follow-up in December 2021 showed a normal CXR without residual respiratory symptoms.

Table 1: Clinical and laboratory data before and after Tocilizumab injection.

Day of Illness	Day 5	Day 6	Day 7	Day 9	Day 10	Day 11	Day 12	Day 13	Day 16	Day 20
Day of Admission	Day 1	Day 2	Day 3	Day 5	Day 6	Day 7	Day 8	Day 9	Day 12	Day 16
White Cell Count (X10^9/L)	12.7	13.0	8.8	17.1		9.7	7.6	5.9		9.4
Absolute Lymphocyte Count (X10^9/L)	2.07	0.9	0.9	0.9		0.6	0.5	0.4		1.8
Urea (mmol/l)	8.8	11.4	13.3	11.6	13.1	15.3	16	16.7	16.8	11.4
Creatinine (µmol/l)	244	297	262	291	243	218	209	201	171	165
EGFR (mL/min/1.73m^2)		16	19	17	21	24	25	26	32	33
ALT (U/L)	75	45	43	92		65	48	42		54
AST (U/L)	37	44		148			26	26		
LDH (U/L)	280	335		527			455	427		
CRP (mg/L)		250.1		139.5			42		6.0	1.7
Ferritin (µg/l)		157.20								
Oxygen Requirement	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No
P/F Ratio (norm >300)				162	145	117	185	260	312.5	

Tocilizumab

ALT: Alanine transaminase; AST: Aspartate aminotransaminase; LDH: Lactate dehydrogenase; CRP: C-reactive protein; VM: Venturi mask; P/F Ratio: Partial Oxygen / Fractional Inspired Oxygen Ratio

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DISCUSSION

KTR is categorized as high-risk group for COVID-19 infection due to chronic immunosuppression. There is no clear guideline on the timing of immunosuppression cessation during acute COVID-19 infection. Some experts recommended should continue to receive their CNIs and prescribed dose of glucocorticoids but their antiproliferative drugs should be stopped. In the minority of KTR with severe COVID-19 infection requiring ICU admission and mechanical ventilation, CNIs and antiproliferative drugs should be immediately withdrawn and glucocorticoid doses should likely be increased. (2) A genome-wide analysis of protein-protein interactions between COVID-19 and human host proteins identified both cyclophilin family members and FK506 binding proteins as interaction partners for COVID-19 proteins. In addition, both FK506 treatment and knockdown of FK506-binding proteins 1A and 1B inhibited SARS-CoV-2 replication in vitro. There is a suggestion that tacrolimus, may have inhibitory potential in COVID-19 viral replication. Although studies did not advocate the use of these drugs for their potential antiviral properties, these findings may support their continuing use as the preferred maintenance immunosuppressant in transplant recipients with COVID-19 infection. (3)On day 9 of illness, we discontinued her immunosuppression therapy as her creatinine and Tacrolimus drug level were rising.

The safety and efficacy of Tocilizumab for treatment of severe COVID-19 infection remained inconclusive, especially among KTR. Tocilizumab initiation was due to worsening clinical conditions, requirement of venturi mask 60%, lymphopenia, without resolution of CXR opacities. Immunosuppression was continued on the day of admission while she remained in stable clinical state.

CONCLUSIONS

Tocilizumab is used in moderate and severe cases of COVID-19 pneumonia where a hyperinflammatory state or CS is present (3). Data related to the use of Tocilizumab are limited but encouraging as no side effect has been reported so far(4,5). More evidence is needed to confirm benefit of Tocilizumab in KTR with severe COVID-19 infection.

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