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Correspondence

Heart-Kidney Transplanted patient affected by COVID-19 pneumonia treated with tocilizumab on top of immunosuppressive maintenance therapy

A 61-year-old Caucasian man presented to the emergent department on April 1st, 2020 due to breath shortening, after 15 days of fever and cough. The patient had received a heart transplantation (HT) in 2005 due to refractory heart failure in dilated cardiomyopathy and a subsequent living-related kidney transplantation in 2015 due to end-stage chronic renal failure on maintenance hemodialysis. Other medical history included hypertension on carvedilol 6.25 mg bid, and furosemide 12.5 mg qd, paroxysmal atrial fibrillation on warfarin and amiodarone 200 mg qd, hypothyroidism on levothyroxine 100 mcg qd. A recent echocardiogram showed preserved biventricular systolic function, and last coronary angiography revealed normal coronary arteries in March 2019. Immunosuppression was maintained with cyclosporine 50 mg bid; mycophenolic acid 720 mg bid and prednisone 2.5 mg qd. On admission day, temperature was 37.5 °C, blood pressure 160/90 mm Hg, heart rate 68 beats per minute, sinus rhythm, respiratory rate (RR) of 24 breaths per minute, and oxygen saturation of 98% while the patient was receiving supplemental oxygen through a nasal cannula at a rate of 2 L per minute. Initial arterial blood gas analysis revealed partial pressure of oxygen (PaO_2) of 71 mmHg with a ratio of the PaO_2 to fractional inspired oxygen (FiO_2) of 253. Before hospitalization he has been treated empirically with azithromycin for 3 days and amoxicillin/clavulanic acid 875/250 mg bid for 7 days. Nucleic acid testing of a nasopharyngeal swab for SARS-CoV-2 virus was positive. Chest computed tomography (CT) revealed diffuse bilateral glass ground opacities compatible with interstitial pneumonia (Supplemental Fig. 1A). Laboratory test in the emergency department revealed normal white blood count of 4.5 * 10^9/L, with 0.27 lymphocytes * 10^9/L significantly increased C-reactive protein (CRP) of 7.8 mg/dL (upper reference limit [URL] of 0.5), without elevation of procalcitonin of 0.16 ng/mL (URL of 0.5). Creatinine value was mildly elevated (1.39 mg/dL) with an estimated glomerular filtration rate of 54 mL/min/1.73 * m^2. On admission day, cyclosporine was continued, while mycophenolic acid was reduced to 360 mg bid and prednisone was increased at 10 mg daily. HCQ 200 mg tds and intravenous (IV) ceftriaxone 2 g daily were started. On day 3 the patient developed an acute respiratory distress syndrome and needed supplemental oxygen through a nasal cannula at a rate of 15 L per minute with a PaO_2 of 85 mmHg and a PaO_2/FiO_2 of 94. The patient was tachypneic (RR of 28 breaths per minute) and a noninvasive ventilation with a FiO_2 of 70% was initiated, reaching an oxygen saturation of 100%. Due to clinical deterioration, the patient was referred to our hospital, a tertiary care center, where the patient had been transplanted. The day the patient was moved to our hospital, he received a dose of IV tocilizumab 600 mg (8 mg/kg based on actual body weight) for worsening respiratory failure, in the absence of signs of bacterial infections. After 12 h a second dose of IV tocilizumab 600 mg was administered as per the off-label protocol adopted in our hospital. On day 1 after tocilizumab, the patient significantly improved, and was weaned off the noninvasive ventilation. Although increase of d-dimer was observed, CRP gradually decreased to 1.4 mg/dL and lymphocytes increased from 0.31 to the 0.59 * 10^9/L in 5 days, while procalcitonin levels remained low. Respiratory function significantly improved in the following days after tocilizumab infusion: need for supplemental oxygen through a nasal cannula decreased from a rate of 10 L to 2 L per minute and the RR decreased from 30 to 16 breaths per minute after 7 days (Table 1). Immunosuppressive regimen was maintained with a target cyclosporine trough level between 80 and 100 ng/mL, and HCQ was suspended on day 11. On day 15 after admission oxygen saturation decreased to 91% after a 6-minute walking test, while it was 96% on 2 L per minute of supplemental oxygen. The SARS-CoV-2 nasal swab RT-PCR turned negative on day 15 and on day 16 when the assay was repeated for confirmation of negative result. A chest high-resolution CT scan was performed before discharge on day 17, revealing residual diffuse ground glass opacities mainly in the right lung (Supplemental Fig. 1B). Echocardiogram performed during the hospitalization confirmed preserved systolic ventricular function. The patient is alive on June 23rd, with an oxygen saturation of 98% on room air and he did not develop any secondary infection after tocilizumab administration.

Limited data on the use and efficacy of tocilizumab for the treatment of transplanted patients with COVID-19 exist [1,2]. In a series from New York, 6 heart transplanted recipients were treated with tocilizumab, and one died, and two were still hospitalized at the time of the end of follow up [3]. Another report described two heart transplant recipients treated with tocilizumab, and one died and while the other survived [4]. This case report shows potential usefulness of tocilizumab administration at the onset of the respiratory failure, before tracheal intubation need, especially when clinical data and laboratory exams do not suggest latent or overt superimposed infections. In fact, the risk of severe infection can be a serious concern particularly in immunosuppressed patients as observed in another published case [4]. We observed

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Table 1
Laboratory values and vital parameters over the COVID-19 clinical course before and after treatment with tocilizumab.

	Reference range, adults	April 1st Day −2	April 2nd Day −1	April 3rd Day 0 (exams before tocilizumab 600 mg)	April 4th Day + 1 (before second dose of tocilizumab 600 mg)	April 6th Day + 3	April 8th Day + 5	April 10th Day + 7
Laboratory exams								
IL-6	<7 pg/mL			82	626	846		
CRP	<0.5 mg/dL	7.8		8.4	7.4	6.2	1.4	
Procalcitonin	<0.5 ng/mL	0.16			0.15	0.05		
d-dimer				0.91		32.76	21.08	
LDH	<220 U/L	395						
WBC	4–10 10 * 9/L	4.5		5.6	2.86	3.27	3.61	3.64
Lymphocytes	0.8–5 10 * 9/L	0.27		0.31	0.42	0.33	0.45	0.59
Hb	14–18 g/dL	14.1		13.6	12.5	12.9	13.2	13.1
Platelets	140–440 **10** * 9/L	241		267	264	270	246	244
ALT	<45 U/L			18	17	15	22	
AST				36	33	27	37	33
Ferritin	<400 ng/mL				497	428	340	
INR		2.23			3.3	3.03	2.72	2.5
Albumin	4.02–4.76 g/dL				2.8			
Creatinine	mg/dL	1.39		0.97	1.16		1.43	1.36
CK	<200 U/L	81			90			
NTproBNP	<194 pg/mL	2590						
cyclosporine	ng/mL					94		85
		April 1st Day −2	April 2nd Day −1	April 3rd Day 0 (before tocilizumab 600 mg)	April 4th Day + 1 (before second dose of tocilizumab 600 mg)	April 6th Day + 3	April 8th Day + 5	April 10th Day + 7
Vital parameters								
Temperature	C	37.5		36.4	36	36	36	36
BP	mmHg	160/90		160/90	140/90	120/70	125/80	130/80
HR	bpm	68		68	60	62	65	55
RR	bpm	24		30	20	18	16	16
O2 sat.	%	98		96	96			
pO2	mmHg	71	85					
PaO_2/FiO_2		253	94		131			
Supplemental oxygen/respiratory support		Nasal cannula 2 L/min	High flow 15 L/min	PEEP 10 FiO2 0.6	Nasal cannula Oxygen 10 L/min	Nasal cannula Oxygen 6 L/min	Nasal cannula Oxygen 4 L/min	Nasal cannula Oxygen 2 L/min

a significant increase of d-dimer after administration of tocilizumab, supporting the need for monitoring d-dimer after administration of this drug, and suggesting the usefulness of anticoagulant agents such as enoxaparin. Our patient was on warfarin due to paroxysmal atrial fibrillation, thus enoxaparin was administered only when INR was below 2. Potential complications after the administration of tocilizumab in COVID-19 patients to be aware of include septic shock, and gastrointestinal perforation [5]. Several studies have showed the potential benefits of tocilizumab, but the results are mainly based on single-center non-randomized experiences with a maximum number of 100 treated patients [5]. In conclusion, this case summarizes the potential efficacy of tocilizumab to treat heart and heart and kidney transplanted recipients affected by COVID-19 severe pneumonia with a background of a maintenance immunosuppressive regimen. Nevertheless, only randomized trials will define the efficacy of tocilizumab and its place, timing and dosing in patients with COVID-19.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2020.100596.

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Enrico Ammirati [a,*]
Giovanna Travi [b]
Carloandrea Orcese [b]
Alice Sacco [a]
Sara Auricchio [c]
Maria Frigerio [a]
Massimo Puoti [b]

[a] *De Gasperis Cardio Center and Transplant Center, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy*
[b] *Division of Infectious Diseases, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy*
[c] *Department of Nephrology and Dialysis, ASST di Monza, Desio, Italy*

* Corresponding author at: Niguarda Hospital, Piazza Ospedale Maggiore 3, 20162 Milano, Italy.
E-mail address: enrico.ammirati@ospedaleniguarda.it (E. Ammirati)

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