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Coronavirus Pandemic

Severe COVID-19 infection in a kidney transplant recipient treated with lopinavir/ritonavir, hydroxychloroquine and dexamethasone

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Abstract

Severe COVID-19 infection management for a recipient of kidney transplant has debatable prognosis and treatment. We described the case of a COVID-19 infected 70 year old female, previously had renal transplantation in 2017. The patient took immunosuppressive agents as routine drugs for transplant recipient status and received lopinavir/ritonavir, hydroxychloroquine, and dexamethasone daily at the hospitalization. Specific question arises about renal transplant recipients being infected by COVID-19 – whether the infection will get worse compared to those without immunosuppresive agent. In this case, author decided to stop the immunosuppressive agent followed administration of combination lopinavir/ritonavir, hydroxychloroquine, and dexamethasone that gives a good clinical impact change to patient's condition after once getting worsened and mechanically ventilated. Nevertheless, the assessment of risk and benefit in continuing immunosuppressive drugs is concurrently essential due to the prevention of transplant rejection.

Key words: COVID-19; kidney transplant; immunosupressive drugs; lopinavir/ritonavir; hydroxycholorquin.

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Introduction

At the end of 2019, a number of cases of pneumonia with unknown etiology emerged in Wuhan, Hubei Province, China. This novel type of pneumonia spread rapidly to the other Chinese districts and provinces and eventually to almost every part of the world. On January 7, 2020, a new type of coronavirus was identified in an oropharyngeal swab sample from one patient by the Chinese Center for Disease Control and Prevention (CDC) and was later named Novel Coronavirus 2019 (2019 n-CoV) by the World Health Organization (WHO) [1,2].

COVID-19 infection majorly presents as an acute respiratory illness with signs of pneumonia yet it can also affect many extrapulmonary organ include heart, kidneys, digestive tract, haematological and central nervous system [3]. Approximately 20% of COVID-19 patients manifest moderate to severe symptoms and 5% fall to critically ill [4]. Risk factor identified for severe disease include age, underlying diseases such as diabetes, hypertension, chronic kidney disease, morbid obesity, coronary heart disease, and chronic lung disease [5]. Solid organ transplant recipients are susceptible of SARS CoV-2 infection because of their chronic immunosuppression to prevent rejection especially diabetes and hypertension [5]. Although renal transplant recipients are susceptible of the virus, only few reports of COVID-19 infection in kidney transplant patient have been published [6].

Specific question arises for renal transplant recipients infected COVID-19, whether the infection will get worse in patients receive immunosuppresive agent and it should be stopped or not [3].

Case Report

A 70-year-old female patient, previously had kidney transplantation in 2017, presented to the Emergency Ward with shortness of breathe one week

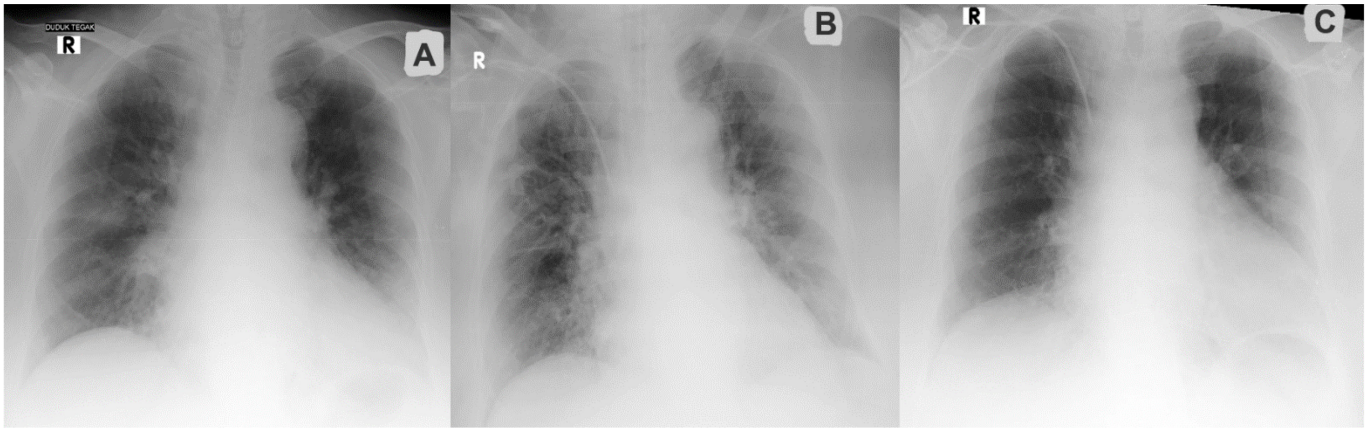
before admission. The patient also reported productive cough, fever and frequent watery diarrhea in the last 1 week. The patient had nausea and decreased appetite but did not report any vomiting. She usually took immunosuppression therapy for her transplantation status with tacrolimus 1 mg twice daily, mycophenolic sodium 180 mg twice daily and methylprednisolone 4 mg once daily. She revealed positive result for COVID-19 from nasal swab using RT-PCR (reverse transcription polymerase chain reaction) after one of members of her family also had been infected and her husband had just passed away a few days prior to admission with a confirmed COVID-19 status. Physical examination at first evaluation was unremarkable with blood pressure of 147/78 mmHg, heart rate (HR) of 98 beats per minute with regular rhythm, strong pulse, and normal amplitude; respiratory rate (RR) of 22 breaths per minute, axillary temperature of 36.9^{o}C, and oxygen saturation was 95% ambient air. Laboratory findings (Table 1) showed normal leucocyte of 4,540 /uL (neutrophils count 61.5% and lymphopenia 9.8%), increased level of CRP (55.3 mg/dl) and ferritin (378.3), normal procalcitonin level (< 0.05) and D-dimer (0.7 ng/ml), kidney function were within normal limit (BUN 15 mg/dl and creatinine serum 0.9 mg/dl). There was moderate hyponatremia (Sodium level 120 mmol/L) and tacrolimus level of 4.3 ng/ml. From chest radiography (Figure 1), there was pulmonary consolidation found in the right perihillar and left paracardial field. The patient was given lopinavir/ritonavir fixed dose combination for fourteen days, hydroxychloroquine for five days, and dexamethasone 6 mg for ten days ahead. Immunosuppressive drugs were continued as usual dose and hyponatremia was treated. On the third day of hospitalization, the patient reported worsening shortness of breath with elevated respiratory rate (28 times per minute) and decreased peripheral capillary oxygen saturation 92%. Laboratory results (Table 1) showed elevation of CRP level (88.8 mg/dl), ferritin (462.50 ng/ml), and tacrolimus level (24ng/ml). Arterial PO_2 level dropped until 58 mmHg. Worsening of the condition in patient made consideration for those of us who care to stop giving her immunosuppressive agent supported by the patient's family confirmation. On the third day hospitalization, tacrolimus and mycophenolate sodium were stopped, the patient was intubated and ventilator was initiated. Heparin therapy was initiated at a dose of 1500 IU in 1 hour followed by 350 IU/hour intravenously.

On the eighth day, there was improvement in chest radiography (Figure 1) and laboratory results (Table 1) and arterial pO2 level increased to 73mmHg. On the thirteenth day of hospitalization, sputum culture was

Table 1. Laboratory Data.

Variable	Reference Range, Adult	On Admission	3rd Day	8th Day	35th Day
Hb (g/dl)	12-16	13	13,9	12,5	12.3
Hct (%)	36-46	39	40,2	37	36.9
White Blood Cell Count (/µL)	4500-11000	4.540	6.840	11.600	19.700
Differential Count (%)					
Neutrophil	40-70	61,5	76,5	75,6	77,9
Lymphocytes	22-44	9,8	10,5	11	11,2
Platelet count (/µL)	150.000-400.000	170.000	195.000	222.000	131.000
Sodium (mmol/L)	135-145	120	133	142	133
Potassium (mmol/L)	3.5-5.0	4	3,6	3,4	4,4
Chloride (mmol/L)	98-108	100	106	110	108
Blood Urea Nitrogen (mg/dl)	8-18	15	13,8	77,4	50,7
Serum Creatinine (mg/dl)	0.6-1.1	0,9	0,72	0,95	1,29
SGOT (U/L)	0-50	44	23	89	31
SGPT (U/L)	0-50	32	19	94	41
Albumin (g/dL)		3,6		3.9	4,0
C-Reactive Protein (mg/L)	< 1,0	55,3	88.8	2.5	100,7
D-Dimer (ng/ml)	< 500	0,7		1696,75	2,6
Tacrolimus (ng/ml)		4,3	24		
Blood Gas Analysis					
pH	7.35-7.45		7,39	7,491	
pCO2 (mmHg)	35-45		35	37,9	
pO2 (mmHg)	80-100		58	73	
HCO3 (mmol/L)	22-26		21,8	29.,2	
BE (mmol/L)	-2 s/d 2		-2	6	
SaO2 (%)	90-100		90	96	
Swab PCR	Negative	Positive	Positive	Positive	Negative 2x

Figure 1. A. Chest X-ray first day hospitalization; **B.** Chest x-ray eight day hospitalization, showing imporvement; C. Chest X-ray thirty-fifth day before discharge from hospital.



positive for *Stenotrophomonas maltophilia* and sensitive for antibiotic moxifloxacin, while no bacterium was found from the blood culture, hence moxifloxacin was initiated later. On the sixteenth day, along with the negative result from the oropharyngeal/nasal swab for COVID-19, the patient was finally extubated. During the course of hospitalization, serum creatinine level slightly increased and there was no rejection from kidney graft (Figure 2). Tacrolimus level was relatively normal throughout the hospitalization. The patient was discharged after thirty-five days of treatment without fever or diarrhea. Her oxygen saturation was 97% ambient air, respiratory rate was 18 times per minute, blood pressure was 130/80 mmHg and there were improvements in laboratory results (Table 1). The oropharyngeal/nasal swab result for COVID-19 remained negative until second examination in the hospital. Hydroxychloroquine and immunosuppressive agents were withheld until patient return for regular checkup at the outpatient clinic.

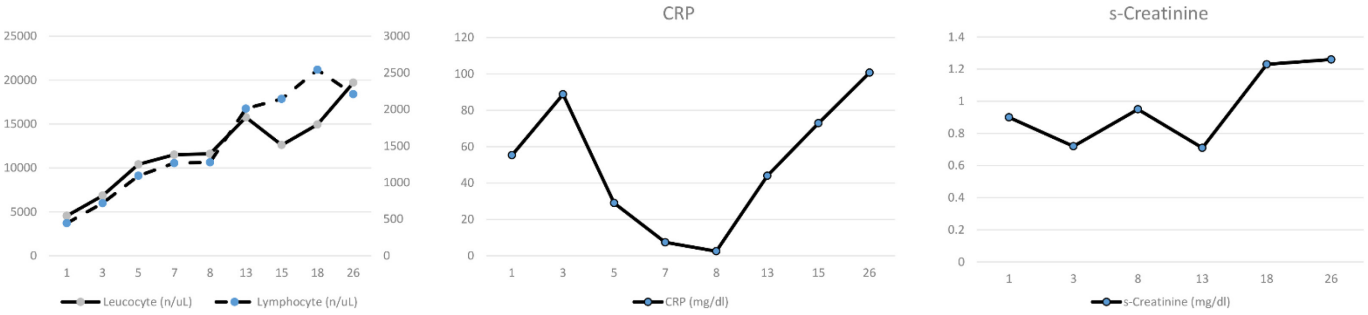
Discussion

By June 2020, SARS-CoV2 has infected more than 45,000 people in Indonesia. The death-case had reached 2,500 cases and COVID-19 comorbid chronic kidney disease categorized as severe case (19.7%) with mortality rate CKD with pneumonia approximately 14-16 higher than population [7,8]. Unfortunately, there were no statistics related to COVID-19 infection in patient with renal transplatation.

Kidney transplant recipients are susceptible of contracting COVID-19 infection due to immunosuppressive conditions, such as chronic kidney disease, diabetes and hypertension. Majority comorbidities found affecting patient progress with COVID-19 infection [3,9,10].

Manifestation of COVID-19 was not very differ from in renal transplant patients include fever, dry cough, and shortness of breath. There are also some dominant atypical presentations such as digestive symptoms and acute confusion or delirium [4]. In this case, a 70-year-old female patient complained shortness of breath that was perceived for 1 week and worsened in the last 1 day, accompanied by productive cough and fever. She also complained of having diarrhea for 1 week, with the following characteristics: mushy stool, experienced 4-5 times/day, with yellowish color. The patient also complained of having nausea and decreased appetite but did not report any vomiting episode.

Figure 2. Trends of leukocytes and lymphocyte counts (absolute number/µL); C-reactive protein (mg/dL); serum creatinine.



The standard therapy for patients with solid organ transplant infected SARS-CoV-2 is debatable. Treating immunosuppression patients with COVID-19 is exceptionally difficult as several factors must be taken considered, including age, severity of COVID-19 infection, related comorbidities, and transplantation-to-infection interval. The usual recommendation for mild to moderate COVID-19 patients with renal transplant is to continue or reduce the dose of immunosuppressive drugs or even stop, regardless it might increase death rate patients positive COVID-19 infection [11,12].

There is currently no strong recommendation regarding managing immunosuppresive drugs in a renal transplant patient with COVID-19 infection, but a study suggests that antiproliferative drugs such as mofetil mycophenolate (MMF) and azathioprine should be discontinued at the time of hospitalization, yet methylprednisolone dose can be adjusted following the tacrolimus dose. In patients with severe infection (needed intubation and mechanical ventilation), it is advisable to completely terminate calcineurin inhibitor therapy while maintaining corticosteroid therapy [9,11]. In our case, after the third day all immunosuppresive drugs were stopped then we switched methylprednisolon into dexamethasone.

At the start of the COVID-19 pandemic, the use of steroids was still being debated. A meta-analysis derived from a combination of four RCTs aimed at evaluating the effect of MP administration for ARDS therapy resulted in a significant reduction in mortality with longer ventilator-free duration. In addition, the hypothesis of the benefits of using steroids in the case of COVID 19 is the occurrence of cytokine storm due to viral infection. Therefore, steroids have a place to reduce these hyper inflammatory effects [13]. Also, The RECOVERY Collaborative study showed that dexamethasone reduces 28-day mortality among patients who were treated with invasive mechanical ventilation nevertheless only one systematic review showed corticosteroid could increase death rate for pneumonia COVID-19 [11,14,15]. In our case, the patient received dexamethasone 6 mg daily because of her critical condition and was treated with mechanical ventilator.

In some viral infections, overactivation of the immune system can result in the overproduction of immune cells and inflammatory cytokines. This process is known as a cytokine storm. Pro-inflammatory cytokines that are elevated in the serum of patients experiencing cytokine storms include tumor necrosis factor α (TNF α), interleukin-1, and interleukin-6. SARS-CoV-2 infection is often associated with increased pro-inflammatory cytokines leading to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [16] This prompted a trial of the anti IL-6 monoclonal antibody drug, tocilizumab, and continuation of steroid in renal transplant patients. Based on this evidence, consideration to continue or stop tacrolimus should be made based on evidence [9].

Nowadays, there is no yet effective antiviral treatment for COVID-19 patients although there is an urgent need for one. Remdesivir, an adenosine analogue and RNA polymerase inhibitor, has broadspectrum activity against members of several virus families including Ebola, SARS-CoV and MERSCoV (Middle East respiratory syndrome coronavirus). Unfortunately, at present time, there is limitation access and use to this drug [17,18]. The other potential drug for COVID-19 is lopinavir/ritonavir. In an in vitro study, lopinavir/ritonavir had been reported to significantly reduce viral load, although further evaluation, although further evaluation is required regarding its efficacy and safety [18,19]. Due to its avalaibility in our case, lopinavir/ritonavir was given to the patient along with standard treatment for COVID-19.

With the rapid development of knowledge and research on COVID 19, the use of lopivia has given various results. Based on a randomized, controlled, open-label trial in China, COVID 19 therapy using lopinavir–ritonavir did not show a difference in clinical improvement time compared to standard therapy (hazard ratio for clinical improvement, 1.31; 95% confidence interval [CI], 0.95 to 1.80). When viewed from 28 days of death, lopinavir–ritonavir therapy is also not much different from standard therapy (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7). Similar to the ITT range of clinical improvement, only one day shorter than standard of care (hazard ratio, 1.39; 95% CI, 1.00 to 1.91) [20]. Nevertheless, other cohort study also from China found severe COVID-19 who were treated with LPV/r within 12 days of the onset of symptoms, clinical improvement was observed in 18/19 patients (94.74%) [21].

The difference in the results of the two studies could be due to the basic characteristics of the study population. In the study by Cao *et al.*, it was found that various comorbidities could be confounders, whereas in the cohort study by Luo *et al.*, the majority of patients did not find any comorbidities. In the end, there is no best therapy for COVID-19, but in this case there is an improvement in therapy with a combination of these drugs.

Chloroquine phosphate or hydroxychloroquine, drug known to exhibit antimalarial property, has its

inhibitory effect on viral replication and its appropriate lung permeability in COVID-19 cases [18]. One clinical trial conducted among 550 patients in Wuhan using hydroxychloroquine vs placebo demonstrated that hydroxychloroquine in a low dose of 2×200 mg a day significantly decreased IL-6 levels. A rebound increase in IL-6 levels was observed once the hydroxychloroquine therapy was terminated. From this study, it can be inferred that the use of hydroxychloroquine will also help with cytokine storms [22]. However, in another observational study involving patients with COVID-19 who had been admitted to the hospital, hydroxychloroquine administration was not associated with either a greatly lowered or an increased risk of the composite end point of intubation or death [23].

Hydroxychloroquine may additionally prevent SARS-CoV-2 from binding with gangliosides, which in turn may inhibit virion contact with the ACE-2 receptor. It can incorporate into endosomes and lysosomes, resulting in an increased pH of intracellular compartments leading to defective protein degradation, endocytosis, and exocytosis needed for viral infection, replication, and propagation [24]. Due to the rapid expansion of COVID-19, nowadays guideline WHO recommend against administering hydroxychloroquine or chloroquine for treatment of COVID-19. Hydroxychloroquine and chloroquine probably do not reduce mortality or mechanical ventilation and may not reduce duration of hospitalization, may increase the risk of diarrhea and nausea/vomiting, a finding consistent with evidence from its use in other conditions. Subgroup analyses indicated no effect modification based on severity of illness. There was no evidence that the addition of azithromycin modified the effect of hydroxychloroquine for any outcome [25].

The incidence of Acute Kidney Injury (AKI) associated with COVID-19 infection accounts for about 15% of patients. Proteinuria and hematuria have also been reported. COVID-19-infected kidney transplant patients are susceptible in developing AKI compared to the general COVID-19 population. This is due to the entry of SARS-CoV 2 through the Angiotensin-converting enzyme 2 (ACE-2) receptor and dipeptidyl peptidase in proximal tubular cells. Injury kidney from COVID-19 patients because of SARS-CoV-2 virus uptake into the proximal tubular epithelium [9]. A cohort study at a renal transplant center in Belgium reported that about 28% of hospitalized kidney transplant patients infected with COVID-19 experienced AKI, of which none required hemodialysis. Moreover, kidney function improves after proper hydration [3]. During course of treatment patient suffer AKI, after proper adequate treatment, we manage to prevent worsening of AKI.

An obvious concern in this subset of population is the risk of transplant rejection which resulted from reduced doses of immunosuppressive drugs, regardless death rate in hospitalized patients with COVID-19, clinicians should focus on assessing the patient in a case-by-case basis for the risks and benefits of continuing immunosuppressive therapy [9].

Conclusions

We reported a case of a kidney transplant recipient infected with severe COVID-19 requiring intensive care, intubation and mechanical ventilation. The clinical symptoms are similar to those reported in the general population. Standard therapeutic strategy and dose adjustment of immunosuppressive drugs were applied to this patient. During treatment, clinicians decide to administer immunosuppressive drugs as routine drugs for organ transplant recipients. Although it has not been confirmed that the use of immunosuppressive agents aggravates the clinical course of COVID-19 patients, patients with comorbidities have severe clinical outcomes. Despite some studies showed no clinical improvement and no reduction viral load from lopinavir/ritonavir over standard of care, lopinavir/ritonavir is still commonly used to treat COVID-19. In our case, combination therapy between lopinavir/ritonavir, hydroxychloroquine and dexamethasone showed positive effect.

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