

Continuous Hemodiafiltration with the oXiris Filter Ameliorates Cytokine Storm and Induces Rapid Clinical Improvement in COVID-19 – A Case Report

Abstract

Delayed interferon secretion and cytokine dysregulation are responsible for the life-threatening acute respiratory distress syndrome (ARDS), multiorgan dysfunction and shock in COVID 19, which closely resembles secondary hemophagocytic lymphohistiocytosis (sHLH). IL-6, a marker of hypercytokinemia in patients with COVID-19 is positively correlated with disease severity, development and progression of ARDS, and mortality. Therapy to either reduce IL-6 or inhibit its action with either non-specific inhibitors of inflammation like dexamthasone or Tocilizumab a specific inhibitor of IL-6 has produced decrease in mortality. We describe a novel method of treatment in a patient with multiorgan involvement in COVID 19, using the oXiris hemofilter which delivers renal replacement therapy while also reducing cytokines like IL-6.

Keywords: COVID cytokine storm, interleukin 6, oXiris hemodiafiltration acute kidney injury

Introduction

Life-threatening acute respiratory distress syndrome (ARDS), multiorgan dysfunction and shock in COVID 19 has been linked to immune dysfunction and cytokine dysregulation, suggesting a role of virally driven hyperinflammation mediated by multiple cytokines including interleukin 6 (IL-6).^[1,2] Therapies to ameliorate the cytokine storm include steroids and Tocilizumab a specific IL-6 inhibitor.^[3,4] Here we describe an extracorporeal therapy that cleared IL-6 and hastened improvement in a patient with acute kidney injury (AKI) and cytokine-mediated inflammation.

Case

A 77-year-old gentleman with chronic kidney disease (CKD) secondary to obstructive uropathy and creatinine of 3 mg% in May 2020, was admitted to hospital on 14th July 2020 with complaints of weakness, loss of appetite for 6 days, cough, fever and dyspnea for 2 days. He had no abdominal pain, diarrhoea, or sore throat. He had undergone a transurethral resection of the prostate in 2015 and had been treated with ertapenem for an

urine infection with *E. coli* in June 2020. Examination revealed a temperature of 100°F, pulse 100/minute, blood pressure 120/80 mm of Hg, respiratory rate of 22/minute and a GCS of 10/15. Auscultation of the chest revealed bilateral rales while other systemic examination was unremarkable. Pulse oximetry revealed an oxygen saturation of 85%, while breathing ambient air, which rose to 95% on 6 liters/min of oxygen by mask.

A chest roentgenogram showed bilateral upper and lower lobe opacities with an air bronchogram and RT-PCR test (dual probe chemistry) on extracted nucleic acid from nasal and pharyngeal swabs, detected SARS-CoV-2 in the sample. Ultrasonography revealed a shrunken left kidney, bilateral hydronephrosis and hydroureter, but no calculus.

The rest of the investigation results are shown in Table 1 and serial blood gas reports with respiratory support settings in Table 2. His initial treatment consisted of 1800 mg of oral favipiravir, cefoperazone sulbactam 1.5 g every 12 hours, heparin 5000 Units subcutaneously every 12 hours and Methylprednisolone 40 mg intravenously twice daily. He was

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Table 1: Investigation results

Parameter	Date							
	14/7	16/7	17/7	19/7	20/7	21/7	23/7	24/7
Hemoglobin (g/dl)	10.3	8.2			7.8			7.0
Total Leukocyte Count/mm ³	7740	10210			7100			14300
Platelets (lakhs/mm ³)	2.17	1.66			1.58			1.68
PT/INR	20.3/30.7 (0.77)							
aPTT	8.8/11.3			55/32		46/31		
Blood urea (mg/dl)	145	79.40	86.1	29.5	35	76.9	153.2	179.8
Serum Creatinine (mg/dl)	11.73	6.54	6.94	1.31	1.16	2.70	4.68	5.27
Serum Na ⁺ (mmol/L)	132	138	141	140	139	133	137	138
Serum K ⁺ (mmol/L)	5.8	3.7	4.6	2.7	3.5	3.7	4.0	4.0
Serum Cl ⁻ (mmol/L)	100	102	102	101	97	97	98	101
CRP	140.12				59.30			36.5
Ferritin	>1200							
D-Dimer	1756 (N<500)							
IL-6 (pg/ml)		240			38			68

Table 2: Arterial blood gas and respiratory support settings

Parameter	14/7 at 6.06 pm	16/7 at 8.31 pm	18/7 at 5.02 pm	20/7 at 7.35 am	21/7 at 8.59 am	25/7 at 8.02 pm
pH	7.321	7.421	7.421	7.34	7.372	7.426
pCO ₂	37.7	32.2	27.6	36.3	40.2	37.7
pO ₂	52.1	111	83.8	142	97.4	93.4
HCO ₃ ⁻	18.9	20.6	17.6	19.1	22.8	24.9
O ₂ saturation	80.7	98.3	96.8	98.6	95.2	97.6
Base excess	-6.1	-3.1	-6.0	-5.7	-1.6	0.4
Respiratory support	Ambient air	HFNC 50 L/ min FiO ₂ =0.5	HFNC 40 L/ min FiO ₂ =0.4	Mask oxygen 8 l/min	Mask oxygen 4 L/min	Ambient air

dialysed for hyperkalemia on the 14th and 15th July for 4 hours each using a polysulfone dialyzer of 1.3 m², blood flow of 300 ml/minute, obtained from an uncuffed internal jugular dialysis catheter and dialysate flow of 500 ml/min on a Fresenius 4008S NG machine. On the 16th of July his GCS decreased to 8/15, he developed myoclonic jerks and was put on high flow oxygen via nasal canula (HFNC). A computerized tomography study of the brain revealed only age related changes. He received injectable Meropenem and 200 mg of Remdesivir. At the time his interleukin 6 level was 240 pg/ml (normal range 0 – 6) and serum creatinine 6.94 mg/dl.

He was taken for hemodiafiltration on the Prismaflex machine with the oXiris hemofilter, with a blood flow of 200 ml/minute, pre blood pump bicarbonate based PrismaSol BD was infused at 1000 ml/hour, dialysate was PrismaSol BD at 1000 ml/hour and post-filter replacement fluid 500 ml of PrismaSol BD per hour. Heparin was infused using the machines pump at 500 Units/hour. Fluid removal was started at 50 ml/hour, increased to 75 ml and then to 100 ml/hour, giving a total effluent dose of 37 ml/kg/hour. After 57 hours of treatment, with a total of 4932 ml of ultrafiltration, the patients oxygen saturation, sensorium

and tachypnoea had improved and he was switched from HFNC to oxygen delivered by mask [Table 2]. The IL-6 level decreased to 38 pg/ml at the end of therapy. On the 21th of July his chest roentgenogram showed decreased opacities, his GCS was 13/15 and his urine output improved to 100 ml/hour. On the 24th of July he was dialyzed for 3 hours, while breathing ambient air. He was transferred out of the ICU on the 25th July 2020, his serum creatinine stabilized at 4.5 mg/dl and he was discharged from the hospital on the 29th of July 2020. At follow-up a month later his serum creatinine remained stable at 4.3 mg/dl, chest roentgenogram was clear and he was asymptomatic.

Discussion

The key step transforming mild disease with SARS –CoV-2 to severe is immune dysfunction driven by delayed interferon secretion and cytokine dysregulation.^[1] The cytokine profile in COVID-19 closely resembles virally triggered secondary hemophagocytic lymphohistiocytosis (sHLH) with increased interleukin-2, 6, 7, granulocyte colony-stimulating factor (G-CSF), interferon- γ (INF- γ) inducible protein 10, monocyte chemoattractant protein1 (MCP-1), macrophage inflammatory protein 1- α (MIP 1- α), tumor necrosis

factor- α (TNF- α), and clinically presents with unremitting fever, ARDS, cytopenias, and increased ferritin.^[2]

IL-6, a marker of hypercytokinemia in patients with COVID-19 is positively correlated with disease severity, development and worsening of ARDS, mortality and extrapulmonary multi-organ failure, including renal, cardiovascular (including fulminant myocarditis), and hepatic failure. Measures to ameliorate the cytokine storm include steroids, IFN, Tocilizumab, Ulinastatin, Hydroxychloroquine, intravenous immunoglobulins and blood purification therapies.^[2-4] Dexamethasone has been shown to reduce mortality in ventilated patients in the RECOVERY trial,^[5] while Tocilizumab has been reported to reduce inflammation in several reports and observational studies, although randomized trial results are still awaited.^[6]

Our patient had bilateral pneumonia, worsening hypoxia, and sensorium, and acute on chronic kidney disease, needed HFNC oxygen and RRT. oXiris is a highly adsorptive membrane with unique four-in-one properties which include cytokine and endotoxin removal *in vitro* and in septic shock patients, renal replacement therapy, and anti-thrombogenic features.^[7] It is pre-grafted with Polyethyleneimine (PEI) and an average of 4,500 UI/m² heparin during manufacturing. The positively charged free amino groups, in particular linear PEI grafting allows it to adsorb large negatively charged molecules, such as endotoxins and cytokines. This unique design makes the combination of renal support, cytokine removal, endotoxin removal, and local anticoagulant treatment possible in a single device, which is simple to use.^[8] Prior studies have shown IL-6 reduction rates of 70 to 93% at 2 hours of extracorporeal treatment of sepsis patients with oXiris.^[9] In our patient a reversal of the clinical syndrome of worsening respiratory failure and encephalopathy was noted after the use of oXiris hemodiafiltration. This was paralleled by a marked reduction in IL-6 levels with a subsequent small rebound. At the same time there was a very good reduction in serum creatinine and CRP, indicating that the inflammation was controlled and adequate metabolic clearance was achieved. A similar result was reported by Padala *et al.*^[7] in a series of 3 cases, who worsened despite all conventional treatment, and 2 of whom gradually improved clinically, and were weaned from ventilation after oXiris hemodiafiltration. They also noted a reduction in SOFA score, CRP, d-dimer and IL-6 in the surviving patients. Similarly Yang *et al.*^[10] on Cox regression analysis noted a survival benefit in ventilated patients receiving CRRT with a variety of hemofilters including oXiris.

Similarly in a study of 60 septic patients, 51 of whom had AKI, between 2011 and 2018, Turani *et al.*,^[11] found that 72 hours of treatment with continuous oXiris hemodialysis, produced a significant improvement in

the MAP, oxygenation index (PaO₂/FiO₂) ($P < 0.01$) and a marked decrease in lactate, creatinine, and SOFA score ($P < 0.0001$). They also noted a 76% reduction in IL-6 levels ($P < 0.0001$), along with a significant reduction in IL-10, procalcitonin and endotoxin. They suggested that the treatment in multiorgan failure decreased both inflammation and the “cytokine driven detrimental crosstalk” with other organs in AKI. As the cytokine storm in Covid 19 is probably driven by multiple cytokines, hemodiafiltration with oXiris which targets all the elevated cytokines may be an effective alternative both to therapies targeting exclusively Il-6 or steroids, which are of definite proven benefit but are non-specific and may have multiple side effects.^[2]

Conclusions

oXiris hemodiafiltration may benefit Covid 19 patients who require both renal replacement therapy and have multiorgan failure secondary to a cytokine storm. Further studies in this regard are required to confirm this.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understand that his name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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