COVID-19 in Kidney Transplant Recipients

Ilaria Gandolfini, MD1, Marco Delsante, MD1, Enrico Fiaccadori, MD, PhD1, Gianluigi Zaza, MD, PhD2, Lucio Manenti, MD1, Anna Degli Antoni, MD3, Licia Peruzzi, MD4, Leonardo V. Riella, MD, PhD5, Paolo Cravedi, MD, PhD6, Umberto Maggiore, MD1

1Dipartimento di Medicina e Chirurgia Università di Parma, UO Nefrologia, Azienda Ospedaliera-Universitaria Parma, Parma, Italy; 2Renal Unit, Department of Medicine, University Hospital of Verona, Italy; 3UO Malattie Infettive, Azienda Ospedaliera-Universitaria Parma, Parma, Italy; 4Pediatric Nephrology Unit, Regina Margherita Children's Hospital, Città della Salute e della Scienza di Torino, Turin, Italy; 5Renal Division, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts; 6Renal Division, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York

Word count: 710

Table : 1
To the Editor

An outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that began in Wuhan, China, has spread rapidly and has already taken on pandemic proportions. After China, Italy is the country with the highest number of cases so far (41,035 confirmed cases according to Dipartimento della Protezione Civile as of March 19, and 3,405 deaths). In Northern Italy, where the current prevalence of confirmed cases has surpassed in some areas 2 per 1,000 people, kidney transplant patients are getting infected and starting to develop coronavirus disease 2019 (COVID-19).

There are only limited data on COVID-19 in transplant recipients. Herein, we report the outcomes of two deceased-donor kidney transplant recipients with COVID-19 pneumonia admitted to the Hospital of Parma (Parma, Italy), between March 2 and 12, 2020. One was a
75-year-old male (patient #1) and the other a 52-yr-old female (patient #2), at 120 and 8 months after transplant, respectively (Table). Symptoms (cough, myalgia, and fever 38-39°C) started 3 and 1 days before admission for patients #1 and #2, respectively. At the time of infection diagnosis, graft function was stable in patient #1, while patient #2 had developed acute kidney injury (AKI). Both patients were on tacrolimus (Tac), steroids, and mycophenolate mofetil. Both patients presented with fever (38-39°C) and dyspnea at admission. Lung CT scan at admission showed typical radiological findings of COVID-19 pneumonia, with extensive bilateral ground-glass opacities in both; specific treatment was started before arrival of nasopharyngeal swab test results (PCR, confirming SARS-CoV-2 infection on day 3 and 2 after symptoms’ onset). Mycophenolate and Tac were discontinued on the day of admission and both patients received hydroxychloroquine (200 mg twice daily) in addition to lopinavir+ritonavir or darunavir+cobicistat. None of the patients were on ACE inhibitors or ARBs. Both patients required non-invasive ventilation, but no patient was transferred to the ICU. Patient #1 developed abrupt worsening of his respiratory conditions over a period of 24 to 38 hours and expired 5 days after admission before intubation. On day 6 after admission, patient #2 showed signs of systemic inflammation (plasmatic IL-6: 108.2 pg/ml; normal range 0-10 pg/mL; Table). After progressive worsening of respiratory conditions requiring non-invasive ventilation and being considered for intubation, the patient received colchicine (1mg on day 8, and 0.5mg/day thereafter) to reduce inflammation, due the unavailability of anti-IL-6 receptor mAb tocilizumab. Anti-retroviral therapy was stopped; 24hrs after colchicine administration, plasmatic IL-6 concentration decreased to 36 pg/ml, and respiratory conditions stabilized. At the time of writing (day 14 after initial symptoms), the patient is alert and stable on non-invasive ventilation positive airway pressure (PaO₂/ FiO₂ 114, respiratory rate 22 rpm, arterial blood pressure 150/90 mmHg, hear rate 105 rpm). Serum creatinine has returned to baseline levels (1.4 mg/dL) and liver function test are normal. Tacrolimus blood trough levels had initially increased to 39.9 µg/L due to interaction with ritonavir and transient liver failure despite holding tacrolimus. On follow-up, Tac trough levels had returned to target range and Tac was resumed on day 12 (blood levels 5.4µg/L on Tac 0.5mg twice daily).
In kidney transplant recipients with COVID-19 who develop extensive pneumonia, which may require intubation, our current therapeutic approach includes stopping the immunosuppressive therapy (using steroids as the only antirejection drugs) to help promote the specific anti-viral immune response.

As the cytokine storm triggered by the coronavirus seems to be particularly responsible for morbidity of COVID-19, withdrawal of antirejection therapy can be associated with exacerbation of inflammatory response to viral infection. Therefore, IL-6 targeting therapies are being proposed to control acute respiratory distress syndrome (ARDS; currently being tested in a randomized trial in China; ChiCTR2000029765). A randomized controlled trial is testing the safety/efficacy of steroids (NCT04273321), but until results are available, broad use of steroids is discouraged.³

Viroporin E, a component of SARS-CoV, forms Ca²⁺-permeable ion channels and activates the NLRP3 inflammasome.⁴ Colchicine prevents NLRP3 inflammasome assembly, thereby reducing the release of IL-1b and other interleukins, including IL-6.⁵ In patient #2, colchicine therapy was associated with a fast decrease of IL6 levels.

In the presented kidney transplant recipients, the course of COVID-19 did not significantly differ from that of non-transplant individuals. Immunosuppression interruption combined to the anti-inflammatory effects of colchicine may have synergized with antiviral therapy and hydroxychloroquine to lower viral replication and minimize the cytokine storm triggered by SARS-CoV-2.

DISCLOSURE

This article is protected by copyright. All rights reserved
The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

REFERENCES

1. Callaway E. Time to use the p-word? Coronavirus enter dangerous new phase. Nature. 2020; 579: 12.
2. Zhu L, Xu X, Ma K, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. Am J Transplant, 2020. Doi: 10.1111/AJT.15869.
3. Russell CD, Millar, JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet. 2020; 395(10223): 473-475.
4. Nieto-Torres JL, Verdiá-Báguena C, Jimenez-Guardeño JM, et al. Severe acute respiratory syndrome coronavirus E protein transports calcium ions and activates the NLRP3 inflammasome. Virology. 2015;485:330-9.
5. Nidorf SM, Thompson PL. Why Colchicine Should Be Considered for Secondary Prevention of Atherosclerosis: An Overview. Clin Ther. 2019;41(1):41-48.
### Table. Patients characteristics at admission.

| Variables                  | Patients #1 | Patients #2          |
|----------------------------|-------------|----------------------|
| Sex                        | M           | F                    |
| Age (yrs)                  | 75          | 52                   |
| Race                       | White       | White                |
| Months post-Tx             | 120         | 8                    |
| Donors                     | Deceased    | Deceased (DCD)       |

**History**

| Primary nephropathy         | Pyelonephritis | Unknown                      |
|-----------------------------|----------------|------------------------------|
| Flu vaccination             | yes            | yes                          |
| Lung disease                | COPD           | no                           |
| Heart disease               | yes            | no                           |
| Hypertension                | yes            | yes                          |
| Cancer                      | no             | no                           |
| Obesity                     | yes            | no                           |

**Vital signs**

| Respiratory rate (rpm)     | 25            | 28                           |
| Heart rate (rpm)           | 101           | 93                           |
| Blood pressure (mmHg)      | 140/70        | 130/70                       |
| \(PO_2/\text{FiO}_2\)      | 276           | 247                          |

**Signs/symptoms**

| Fever (T > 37.5°C)         | yes           | yes                          |
| Dyspnea                    | yes           | yes                          |
| Diarrhea                   | no            | yes                          |
| Myalgias                   | yes           | yes                          |
| AKI                        | no            | yes                          |
| CT (% of lung involvement) | 40%           | 50%                          |
| Positive swab test         | yes           | yes                          |

**Biochemistry**
| Test                      | d0       | d3       | d7       | (baseline creatinine) | (1.3) |
|---------------------------|----------|----------|----------|------------------------|-------|
| s-Creat (mg/dL)           | 2.2      | 2.2      | NA       | 2.4                    | 3.4   |
| (baseline creatinine)     | (2.1)    |          |          |                        |       |
| PTL (x10^3/mmc)           | 164      |          | 386      |                        |       |
| WBC(x10^3/mmc)            | 6.56     |          | 2.54     |                        |       |
| Lymphocytes (cells/mmc)   | 880      |          | 650      | NA                     |       |
|                          | 110      |          | 120      | 50                     |       |
| Hb (g/dL)                 | 11.7     |          | 11.6     |                        |       |
| d-dim (ng/mL)             | NA       |          | 832      |                        |       |
| AST(IU/mL)                | 45       |          | 62       |                        |       |
| ALT (IU/mL)               | 25       |          | 26       |                        |       |
| LDH (IU/mL)               | 301      |          | 718      |                        |       |
| CPK (IU/mL)               | 82       |          | 197      |                        |       |
| CRP (mg/L); d0, d3, d7    | 180      |          | >20      | NA                     |       |
| Procalcitonin (ng/ml)     | 1.29     |          | 0.98     |                        |       |

**Concurrent/previous relevant therapy**

| Induction therapy         | Thymo    | Thymo    |
|---------------------------|----------|----------|
| Maintenance               | Tac, MMF, St | Tac, MMF, St |
| ACEi                      | no       | no       |
| ARB                       | no       | no       |

**Immunosuppression withdrawal**

| Tac                       | yes      | yes      |
|---------------------------|----------|----------|
| MMF                       | yes      | yes      |
| Steroids                  | no       | no       |

**Antiviral/antibiotics**

| Antibiotics               | yes      | yes      |
|---------------------------|----------|----------|
| Hydroxychloroquine        | yes      | yes      |
| Lopinavir/ritonavir       | yes      | no       |
| Darunavir/cobicistat      | no       | yes      |
| Remdesivir | no | no |
|------------|----|----|

**Outcomes**

| NIV | yes | yes |
|-----|-----|-----|
| ICU | no  | no  |
| Death | yes | no |
| (days after admission) | (5) | (8) |

Abbreviations: yrs, years; AKI, Acute Kidney Injury; CT Computerized Tomography; s-creat, serum creatinine; PTL, platelets; WBC, white blood cells; Hb, haemoglobin; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; LDH, Lactate Dehydrogenase; CPK, Creatine Phosphokinase; CRP, C-reactive Protein; ACEi, ACE inhibitor; ARB, Angiotensin II Receptor blocker; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; St, steroids; NIV non-invasive ventilation; ICU, intensive care unit. NA, not available.