The Challenge of Treating Kidney Transplant Recipients Infected with COVID-19: Report of the First Cases in Israel

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KEY WORDS: coronavirus disease-19 (COVID-19), immunosuppression, kidney transplantation

IMAJ 2020; 22: 602–604

Management of patients in the corona virus era is an ongoing learning process, with few guidelines and day-to-day assessments and revisions. Sharing personal experience is of particular importance. The treatment of solid organ transplant recipients is challenging given the inherent state of immunosuppression. We describe treatment and outcome of the first two kidney transplant recipients infected with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Treatment decisions were made solely on clinical judgment and before recommendations of various experts and organizations were published.

The worldwide pandemic of the coronavirus disease-19 (COVID-19) outbreak is changing every aspect of our lives. Specifically, transplant physicians are faced with many uncertainties, one of them being how to determine the correct immunosuppression regimen for patients with suspected or confirmed COVID-19. The medical community traditionally relies on evidence based medicine, but during this epidemic physicians are relying on expert views and clinical judgment. All shared experience is helpful.

The first COVID-19 patient in Israel was identified in February 2020. The first critically ill patient was reported on 7 March 2020. As of September 2020 more than 230,000 patients have been identified. We add our experience to the accumulating data for managing kidney transplant recipients infected with SARS-CoV-2. In this article, we describe the first two cases of transplant patients diagnosed with COVID-19 and treated in Israel.

PATIENT DESCRIPTION

PATIENT 1

A 52-year-old women, 24 years after receiving a living-related kidney transplantation from her husband, presented to our department. Her kidney disease was presumably chronic glomerulonephritis. Immunosuppressive medication consisting of prednisone 5 mg, mycophenolate mofetil (MMF) 500 mg, and tacrolimus 1 mg twice daily had been prescribed. During the second week of March she attended a large community celebration and was in proximity of a confirmed COVID-19 patient. A few days later she experienced fever up to 38°C and myalgia. On admission to our hospital she was hemodynamically stable (blood pressure 128/70 mmHg). PO_2 saturation was 96% while breathing room air. Laboratory investigation revealed mild acute renal failure with a serum creatinine of 1.12 mg/dl, mild lymphopenia (18% of total white blood cells, absolute count 1000 cells/μL), C-reactive protein (CRP) levels were 10 times above normal levels. Liver function tests and creatine phosphokinase were within normal limits, as was a chest X-ray. A throat swab polymerase chain reaction (PCR) for COVID-19 was positive. She was not treated with any agent (such as plaquenil or azithromycin). Treatment with MMF was withheld. Prednisone dosage was increased to 10 mg a day and the tacrolimus dose was not changed. The patient had an uneventful course, was followed closely, and after 8 days when PCR for COVID-19 was negative she was discharged from the hospital. MMF was re-administrated. Creatinine at that point returned to her previous value of 0.96 mg/dl. Of note, IgG levels for COVID-19 (Euroimmun anti SARS-Cov-2 IgG, Leubeck, Germany) were negative 4 days after discharge.

PATIENT 2

A 62-year-old male, 5 years after undergoing a living donor kidney transplantation, presented to our department. Additional co-morbidities included hyperlipidemia and gout. Maintenance immunosuppressive medications consisted of prednisone 5 mg, mycophenolic acid 360 mg twice daily and tacrolimus 1.5 mg and 1 mg, morning and evening, respectively. The patient was admitted after experiencing seven days of fever up to 39.2°C, myalgia, and diarrhea. On admission he was tachycardic, but oxygen saturation was normal while breathing room air. Chest X-ray demonstrated bilateral infiltrates. Mild acute kidney injury was present with serum creatinine of 1.5 mg/dl. CRP was 18 times the upper limit of normal. He tested positive for COVID-19. He was treated with azythromycin, and no changes were made in his immunosuppressive regimen, other than a small increase of prednisone to a stress dose of 10 mg per day. After 6 days of hospitalization he was discharged with a creatinine of 1.1 mg/dl (baseline levels). COVID-19 IgG levels were detected in this patient.

COMMENT

There are reports about solid organ transplantation recipients infected with COVID-19. Zhu et al. [1] described the first known kidney transplant recipient infected with COVID-19 who recovered from pneumonia. This 54-year-old man, who underwent transplantation 12 years earlier, was managed with intravenous (IV) methylprednisolone and intravenous immune globulin (IVIG), while all oral immunosuppression was discontinued for approximately 18 days and reinstituted after recovery was clinically and laboratory confirmed.

Researchers in Italy reported two additional kidney transplant patients. The treating physicians withheld tacrolimus and MMF, and steroids were continued. In these cases, one patient sadly experienced disease progression resulting in death. Li et al. [2] treated two heart transplant patients with confirmed COVID-19 infection. One of these patients was treated with IV steroids and IvIg while withholding all other immunosuppression. There is no information on the immunosuppressive regimen of the second patient. Both patients recovered uneventfully. Reports on liver transplant recipients are less encouraging. Bhoori et al. [3] provided important insights with a case series suggesting poor outcome and death is related to co-morbid factors and not to the degree of immunosuppression. In their report, older liver transplant recipients with minimal immunosuppression were at higher risk for death when compared to a younger, short-term transplanted cohort of patients. This finding is in accordance with a previous report on pediatric liver transplant recipients and pediatric patients with other immunocompromised states with a favorable outcome.

In March–April 2020, Italy reported a prevalence of infection four times higher (0.37%) in transplant patients than in the general population. No specific information regarding managing immunosuppression was discussed.

The University of Washington, USA, shared its international registry. Regarding changes in maintenance immunosuppression, treatment changes were made for 70% of patients, mainly reducing or stopping the antimetabolite component of treatment, as we chose to do. Columbia University in New York reported 46 kidney transplant recipients infected with COVID-19, and the antimetabolite component of treatment was the first aspect to be changed [3].

Infection is the second leading cause of death in renal transplant recipients. The general approach to the infected transplant recipient considers time from transplantation, type of induction protocol, degree of immunological sensitization, and the severity of the infection (life threatening, moderate infection, or mild infection).

Specific recommendations for the COVID-19 pandemic were published on 6 April 2020 by the EDTA-ERA [4], after our two patients had been discharged. The patients described in our report had a low National Early Warning Score (NEWS2) score (Patient 1 had a score of 1, and Patient 2 had a score of 2). Both had been long-term transplant patients with a stable immunosuppression regimen and no significant cardiac or pulmonary co-morbidities. These clinical parameters, accompanied by the fact they were closely and daily monitored, led to our decision not to withhold all immunosuppression.

It is reasonable to consider changing immunosuppression with different clinical scenarios, and one should understand that clear recommendations or guidelines are lacking. In more severe cases the therapeutic dilemma may be more challenging. In COVID-19 infection, the cytokine storm triggered by the virus is considered a major contributor to morbidity; therefore, withdrawal of immunosuppression in severely ill patients may be a double-edged sword. In fact, IL-6 targeting therapies are undergoing evaluation in the treatment of critically ill patients. When considering management of glucocorticoids, many physicians tend to increase the dose in the case of infection in the transplanted patient. The U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) recommend that glucocorticoids not be routinely administered to patients with COVID-19 unless there is a separate evidence-based indication (e.g., asthma exacerbation). This recommendation is weak and is based on lack of benefit in patients with other types of viral corona-related pneumonia (e.g., previous SARS or MERS epidemics). The management recommendations from the Israeli COVID-19 task force [4] are to consider treatment with systemic steroids in patients at high risk of deterioration. In the first published cohort of Israeli COVID-19 patients there were specific consideration of an immunosuppressed cohort [5].

We find it difficult to recommend a protocol for managing transplant patients with moderate to severe COVID-19 infection, and there is no evidence from randomized clinical trials that any potential therapy improves outcomes in patients with COVID-19 infection. In our opinion, if high dose steroids are used, it may be safe to temporarily withhold the other components of anti-rejection therapy (i.e., calcineurin inhibitors and antimetabolites).

Finally, it is interesting to note the different serologic response in the two patients we described. While the first patient failed to develop anti-COVID-19 IgG antibodies, the second patient was seropositive. It is premature to speculate the significance of this finding, but it will be interesting to test whether the results were related to severity of illness. The seropositive patient was clinically sicker (i.e., higher fever, higher CRP levels, findings on chest X-ray). It will also be interesting to see if it correlated to the existence of other anti-viral antibodies as anti CMV, EBV, HBV or anti- Influenza antibodies. Ongoing data collection and analysis may shed light on this issue.

CONCLUSIONS

We were fortunate to treat stable patients in good clinical condition. We suggest that for patients with mild clinical dis-

ease it is possible to only minimally, or not at all, modify the immunosuppressive treatment they are given as long as the medical team closely follows the relevant clinical parameters of disease activity. In this time of global uncertainty, sharing personal experience is crucial, and should be encouraged, considering the limitations of these personal communications.

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Capsule

A peripheral immune signature of responsiveness to PD-1 blockade in patients with classical Hodgkin's lymphoma

PD-1 blockade is highly effective in classical Hodgkin lymphomas (cHLs), which exhibit frequent copy-number gains of *CD274* (*PD-L1*) and *PDC1LG2* (*PD-L2*) on chromosome 9p24.1. However, in this largely MHC-class-I-negative tumor, the mechanism of action of anti-PD-1 therapy remains undefined. **Cader** and colleagues utilized the complementary approaches of T cell receptor (TCR) sequencing and cytometry by time-of-flight analysis to obtain a peripheral immune signature of responsiveness to PD-1 blockade in 56 patients treated in the CheckMate 205 phase II clinical trial (NCT02181738). Anti-PD-1 therapy was most effective in patients with a diverse baseline TCR repertoire and an associated expansion of singleton clones during treatment. CD4+, but not CD8+, TCR diversity significantly increased during therapy, most strikingly in patients who had achieved complete responses. In addition, patients who responded to therapy had an increased abundance of activated natural killer cells and a newly identified CD3−CD68+CD4+GrB+ subset. These studies highlight the roles of recently expanded, clonally diverse CD4+ T cells and innate effectors in the efficacy of PD-1 blockade in cHL.

Nature Med 2020; 26: 1468

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Capsule

Remodeling senescent blood vessels

The retina is a thin layer of nervous tissue at the back of the eye that transforms light into neuronal signals. The retina is essential for vision and is supported by networks of blood vessels. In diabetic retinopathy, a common cause of vision loss, these microvessels degenerate and regrow in an aberrant manner. Such degeneration and regrowth can compromise the functioning of retinal nerve cells. **Binet** and colleagues observed that, after rapid proliferation, vascular endothelial cells in diseased blood vessels engaged molecular pathways linked to cellular. Senescent vascular units summoned an inflammatory response in which neutrophils extruded neutrophil extracellular traps onto diseased vessels to remodel them. This endogenous repair mechanism promoted the elimination of senescent blood vessels and could lead to beneficial vascular remodeling.

Science 2020; 369: eaay5356

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Never let your sense of morals get in the way of doing what's right.

Isaac Asimov (1920–1992), American writer and professor of biochemistry, known for his works of science fiction and popular science