A review of the evidence for and against the use of steroids in renal transplant patients with COVID-19

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Coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was primarily recognized as a flare-up of respiratory illness ranging from mild to severe cases in China in December 2019.

According to the Centers for Disease Control and Prevention (CDC),1 COVID-19 poses a high risk to renal transplant recipients due to the immunosuppressed state induced by transplant medications. Common symptoms in renal transplant patients with COVID-19 are fever, diarrhea, and respiratory symptoms.

Renal transplant patients infected with COVID-19 have a higher risk of 30-day mortality than non-transplant patients (17.9% versus 11.4%, according to one study).2 Another study showed an overall mortality rate of 20% in organ transplant patients versus 4-14% mortality in non-transplant COVID-19 patients.3

There have been limited reports on graft rejection in renal transplant recipients who received a diagnosis of COVID-19. However, one case report described a 56-year-old patient who experienced antibody-mediated rejection 4 weeks after COVID-19 infection.4 An examination revealed sphere-shaped spiked units in the glomerular capillary indicative of an established COVID-19 infection within the kidneys.

Multiple recommendations and guidelines have suggested discontinuing calcineurin inhibitors, including tacrolimus and cyclosporin, in transplant patients infected with coronavirus.5

On the other hand, growing evidence suggests that severe COVID-19 leads to mortality due to cytokine storm syndrome.6 Thus, immunosuppressive medications may have a good effect on transplant patients with COVID-19.

Corticosteroids are a keystone of many immunosuppressive regimens, including induction therapy, maintenance immunosuppressive therapy, and treatment of graft rejection; however, their use in COVID-19 is controversial.

The purpose of this review is to study the available evidence and guidelines regarding the use of corticosteroids in kidney transplant recipients infected with COVID-19 and to assess the evidence for and against their use in such patients.

A review of English-language articles was carried out using Scopus, PubMed from January 1st, 2020 to July 31st, 2021. Keywords included COVID-19, renal transplant, steroids, corticosteroids, immunosuppression and, Coronavirus. The search resulted in 15 articles most of which were case reports and case series.

Corticosteroids have been a cornerstone of many renal transplant protocols since the 1960s.7 They play a vital role in all phases of transplantation, including induction therapy, maintenance immunosuppressive therapy, and treatment of graft rejection. However, the widespread use of steroids has drawbacks, including metabolic complications, cosmetic changes, cardiovascular events, and deleterious effects on pediatrics growth. Thus, some healthcare centres have adopted steroid-free or steroid-minimal protocols, especially for pediatrics patients.7

Evidence supporting the continued use of steroids in renal transplant patients with COVID-19. Generally, the approach to managing acute COVID-19 in renal transplant recipients is similar to that in non-renal-transplant patients. Many solid organ transplant experts maintain or increase corticosteroid dosage in cases of COVID-19 infection. This practice is supported by many studies,8-11 including the following: RECOVERY is a multi-center, randomized clinical trial conducted on hospitalized patients with suspected or confirmed COVID-19 that included more than 6,000 patients who received systemic steroid treatment with dexamethasone for 10 days or until discharge. This patient population did not include renal transplant patients, but the outcome was in favor of using steroids. The dexamethasone group showed a lower mortality rate and yielded a great benefit for those on mechanical ventilation. Data from a meta-analysis of 7 randomized trials showed reduced mortality among critically ill COVID-19 patients who received steroid treatment.

Disclosure. Author have no conflict of interests, and the work was not supported or funded by any drug company.

Keywords: renal transplant, COVID-19, steroids, Coronavirus

Saudi Med J 2021; Vol. 42 (10): 1149-1152
doi: 10.15537/smj.2021.42.10.20210551
Similar outcomes were observed in Metcovid and CoDEx trials. Infectious Diseases Society of America guidelines suggest using steroids to treat patients hospitalized with severe COVID-19, including those with an oxygen saturation level under 94% on room air and those admitted to the ICU mechanical ventilation or for treatment for septic shock or extracorporeal membrane oxygenation.12

Table 1 shows studies in which steroids were used to treat renal transplant patients with COVID-19, the majority of which showed positive outcomes.

Table 1 - Cases of kidney transplantation patients infected with Corona virus-19 on steroidal therapy

| Type of study/Ref | Age (y) | N | G | Time from transplantation (y) | Maintenance IS | Continued steroid? | Setting | Outcomes |
|-------------------|---------|---|---|------------------------------|---------------|-------------------|---------|----------|
| Cohort trial¹⁴    | 51-64   | 20 | M, F | Median 13                   | Withdrawn all IS started on methylpred 16 mg | Yes | 6 mild hospitalized | 6 patients developed AKI 5 patients died |
| Case report¹⁵     | 65      | 1 | M | Unknown                      | TAC, MMF, Pred | Yes | Severe ICU         | Recovery after 10 days |
| Case series¹⁵     | 21-8    | 8 | F | 0.3                          | TAC, Pred     | Yes | Inpatient          | Recovery Discharged after 2 days |
|                   | 71      | M | 3 | TAC, Pred                    | Yes           | Inpatient         | Discharged after 2 days with stable kidney function |
|                   | 50      | M | 0.2 | TAC reduced dose, Pred      | Yes           | Self-isolation    | Full recovery |
|                   | 63      | M | 15 | TAC, Pred                   | Yes           | Inpatient         | Recovery discharged after 7 days |
|                   | 47      | F | 0.4 | TAC, Pred                  | Yes          | Severe ICU        | AKI recovery, discharged after 21 days |
|                   | 71      | F | 15 | TAC, Pred                  | Yes           | Inpatient         | Discharged after 4 days with full recovery |
|                   | 40      | F | 3  | TAC, Pred                  |               |                   |         |
| Systematic review¹⁵| 31-75   | 554 | M, F | Range: 0-25               | TAC reduced dose, Pred CN: withdrawn in 31.9%, reduced in 19.7%, AD: withdrawn in 75.3%, reduced in 9.5% 72% were on Pred Cyclosporin, MMF, methylpred | Yes | Ranging from home isolation to ICU admission | Renal graft function remained stable in 76.17% of patients, whereas 8.84% experienced graft loss and 1.44% developed AKI. 21.84% of patients died Recovery after 13 days |
| Case report¹⁶     | 29      | 1 | M | 1.2                         | D/C all IS, Started on methylpred 40 mg 97% were on Pred Cyclosporin, MMF, methylpred | Yes | Inpatient         | Recovery after 5 days |
| Case report¹⁷     | 61      | 1 | F | 16                          | MMF, Pred     | Yes | Inpatient         | Recovery discharge after 13 days |
| Case report¹⁸     | 52      | 1 | M | 12                          | D/C all IS, Started on methylpred 40 mg 97% were on Pred Cyclosporin, MMF, methylpred | Yes | Inpatient         | Recovery after 5 days |
| Case report¹⁹     | 50      | 1 | M | 4                           | Pred continued TAC and everolimus withdrawn | Yes | ICU             | Still in ICU at time of report |
| Case report²⁰     | 75      | 2 | M | 10                          | TAC, MMF, D/C | Yes | Severe inpatient  | Died after 5 days  AKI discharge on day 14 |
| Case report²¹     | 52      | F | 0.8 |                             |               | Yes | Severe ICU        | Died with multiorgan dysfunction |
| Case report²²     | 58      | 1 | M | 11                          | MMF and steroid | Yes | Inpatient         | AKI resolution and discharge |
| Case report²³     | 32      | 1 | M | 2                           | MMF, increased dose Pred, TAC | Yes | Inpatient         | AKI resolution and discharge |
| Case report²⁴     | 28      | 1 | F | 0.5                         | MMF, TAC, Pred | Yes | Mild inpatient    | Discharged with full recovery |
| Systematic review²⁵| 21-80   | 561 | M, F | 0-31                       | Outcome n=144: 84 patients increase steroid dose, 6 patients either reduced or DC, 45 patients with no change | Variable | 73 severe inpatients 40 ICU | Outcome reported for 144 patients: 74 patients discharged 36 improved still in hospital, 34 died |
| Cohort study²⁶    | 53.8    | 38 | M | Median 5.8                  | 84.2% on TAC, 89.5% on MMF, 81.6% on Pred. Adjunct steroid boluses were provided for ARDS | Yes | 38 hospitalized: severe ICU 20 patients survived 11 patients died | 27 patients survived 11 patients died |

Ref: reference, N: number of patients, G: gender, M: male, F: female, IS: immunosuppression, ICU: intensive care unit, MMF: mycophenolate mofetil, TAC: Tacrolimus, Pred: prednisolone, CNI: calcineurin inhibitors either tacrolimus or cyclosporin, AD: antimetabolite drugs including mycophenolate and azathioprine, AKI: acute kidney injury, D/C: Discontinued, methylpred: methylprednisolone, EVE: everolimus, ARDS: acute respiratory distress syndrome, IV: intravenous
The National Saudi Ministry of Health Protocol for suspected or confirmed COVID-19 cases. The National Saudi Guidelines for managing COVID-19 infection support the use of steroids in patients infected with COVID-19, ranging from the use of inhaled budesonide in cases of new cough onset to the administration of systemic dexamethasone in severe cases requiring supplemental oxygen.

The National Institutes of Health COVID-19 Treatment Guidelines recommended treating renal transplant patients infected with COVID-19 in exactly the same way as non-transplant patients when it comes to the use of dexamethasone; however, they pay more attention to the use of tocilizumab with dexamethasone because both exhibit immunosuppressive effects and expose the patients to a risk of secondary infections.²⁴

British guidelines on the management of transplant recipients diagnosed with or suspected of having COVID-19 suggest using a high dose of steroids to treat progressive pulmonary disease, and maintaining steroid dosage in cases of otherwise mild disease without increasing it.²⁵

Evidence against using steroids (evidence for use of a steroid-sparing regimen) in COVID-19 patients. Data from a case report shows that a patient was treated successfully with a steroid-free regimen and a slight reduction in the dosage of other maintenance immunosuppression medications.²⁶ The authors explain that steroid use may hinder immunity, diminish virus clearance, and intensify coronavirus shedding. However, the available evidence shows that the benefits of steroid use outweigh the risks.

In conclusion steroids are recommended to treat severe COVID-19 symptoms in renal transplant recipients at increased risk for contracting COVID-19 and for developing severe COVID-19 due to their immunocompromised state, especially those who require mechanical ventilation or supplemental oxygenation. On the other hand, steroid use is discouraged in patients with mild COVID-19 who do not require oxygen therapy. All patients who require steroid therapy should be monitored during steroid treatment for side effects, including hyperglycemia and secondary infections.

Protocols for optimal maintenance of immunosuppressive therapy in renal transplantation have not been fully established. The maintenance of immunosuppression medications during COVID-19 infection is frequently modified by either stopping or reducing antimetabolite use followed by the use of calcineurin inhibitors and maintenance of a steroid dose; however, the benefits associated with the reduction of immunosuppression medications must be carefully weighed against the risk of graft rejection.

Acknowledgment. The authors gratefully acknowledge Scribendi (www.editage.com) for the English language editing.

Received 7th July 2021. Accepted 24th August 2021.

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