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https://doi.org/10.1016/j.nefro.2023.05.005

Real-world experience with mild-moderate COVID-19 therapies in kidney transplant patients: How to treat patients with chronic kidney disease from now on?

Experiencia en vida real con terapias frente a COVID-19 leve-moderado en trasplantados renales: ¿cómo tratar a partir de ahora a los pacientes con enfermedad renal crónica?

Dear Editor,

In recent months, recommendations for the treatment of non-hospitalized patients with mild-moderate COVID-19 and high risk of progression to severe disease included several antiviral drugs (nirmatrelvir/ritonavir, remdesivir and molnupiravir) and monoclonal antibodies (mAB) (primarily sotrovimab in Europe).[1] However, there is little documented real-life efficacy in renal transplant (RT) recipients.[2,3]

We conducted a retrospective cohort study of all RTs with mild-moderate COVID-19 during the period January 1, 2022, to December 31, 2022, who received outpatient treatment in our hospital area. We defined mild-moderate COVID-19 when patients had symptoms related to SARS-CoV-2 infection (diagnosed by PCR and/or antigen) without an indication for hospital admission. We defined severe COVID-19 if patients required hospitalization or died. The indication for drug treatment was made according to known risk factors for disease progression: age > 60 years and/or post-RT time < 2 years and/or comorbidities. The choice of drug depended on anti-S IgG titers (< 1.000 BAU/ml: sotrovimab) and estimated glomerular filtration rate (eGFR) (>30 ml/min/1.73 m^2: remdesivir in 3 day regimen; <30 ml/min/1.73 m^2: molnupiravir). We did not consider using nirmatrelvir/ritonavir because of the strong drug interactions described with immunosuppressive drugs. Additionally, we collected data from all RT patients requiring hospitalization for COVID-19 during the study period, both treated and untreated prior to admission, as the comparison group.

During 2022, 107 RT patients with mild-moderate COVID-19 received outpatient treatment (sotrovimab n = 63, remdesivir n = 34, molnupiravir n = 10) (Table 1). A total of 83.8% were vaccinated at the time of infection according to guidelines provided by Ministry of Health. There were no differences in patient characteristics or clinical manifestations in relation to the drug received, except for the indication criteria for each drug (renal function, anti-S IgG).

In addition, 37 RT patients were hospitalized throughout the year for COVID-19. Only 3 of them had previously received outpatient treatment (sotrovimab n = 2, molnupiravir n = 1); the rest did not previously contact their RT doctor and already had severe COVID-19 when they attended the hospital, requiring admission. When comparing the recognized risk factors for progression to severe COVID-19, we found no differences between the two groups, treated and not treated, on an outpatient basis (Table 2). Five patients died, all of them in the group that had not received outpatient treatment.

We present the largest series of RT patients with mild-moderate COVID-19 treated on an outpatient basis. Our results suggest that early anti-COVID-19 therapies can halt the progression to severe disease in high-risk patients. Very few of the patients treated as outpatients required admission and none died. Patients admitted without prior treatment had risk factors for the development of severe COVID-19 similar to those in the outpatient group. Considering the favorable evolution

DOI of original article:
https://doi.org/10.1016/j.nefro.2023.06.007.

Table 1 – Characteristics of patients treated by anti-COVID-19 therapy.

	Total (n = 107)	Sotrovimab (n = 63)	Remdesivir (n = 34)	Molnupiravir (n = 10)	p
Male, n (%)	52 (48.6)	27 (42.9)	18 (52.9)	7 (70)	0.232
Age (years), mean (SD)	59.5 (14.3)	60.2 (15.3)	57.4 (13.7)	62 (10.4)	0.607
Time post-RT (months), median [RIQ].	59.5 [29.2, 186.7]	121 [11.2, 217.2]	58 [29.2, 117.5]	37.1 [8.5, 152.1]	0.461
Diabetes mellitus, n (%)	40 (37.4)	26 (41.3)	11 (34.4)	3 (30)	0.692
eGFR (ml/min/1.72 m^2)[a], median [RIQ].	42.6 [25.8, 58.1]	40.8 [21.9, 50.9]	49 [41.1, 68.8]	27.2 [12, 39.4]	<0.001
Respiratory clinic, n (%)	87 (81.3)	51 (81)	28 (84.8)	8 (80)	0.880
Fever. n (%)	31 (29)	19 (30.2)	11 (33)	1 (10)	0.353
Digestive clinic. n (%)	8 (7.5)	5 (7.9)	3 (9.1)	0	0.624
Dyspnea, n (%)	4 (3.7)	2 (3.2)	2 (6.1)	0	0.628
COVID-19 vaccination, n (%)[b]	88 (83.8)	53 (84.1)	25 (78.1)	10 (100)	0.259
Seroconversion (>259 BAU/mL), n (%).[c]	53 (49.5)	22 (34.9)	23 (71.9)	8 (80)	0.001
IgG anti-S (BAU/mL), median [RIQ].	18 [16.8]	353 [109.7, 787.5]	1504.4 [961.1, 4176.5]	2124.5 [391.25, 2765]	<0.001
Progression to severe COVID-19, n (%)[d]	3 (2.8)	2 (3.1)	0 (0)	1 (10)	0.240

[a] eGFR: glomerular filtration rate estimated according to the CKD-EPI equation.
[b] According to the vaccination schedule indicated by the Ministry of Health at the time of infection.
[c] Considered as humoral response (anti-S IgG > 259 BAU/ml) at the time of infection.
[d] Defined as need for hospitalization due to COVID-19.

Table 2 – Comparison of characteristics and evolution of patients with outpatient treatment vs. untreated patients.

	No outpatient treatment (n = 34)	With outpatient treatment (n = 107)	p
Male, n (%)	18 (52.9)	52 (48.6)	0.211
Age (years), mean (SD)	63.1 (13.2)	59.2 (14.3)	0.185
Time post-RT (months), median [RIQ].	54 [24.5, 101.5]	59.5 [29.2, 186.7]	0.932
Diabetes mellitus, n (%)	11 (35.5)	40 (38.1)	0.792
eGFR (ml/min/1.72 m^2), median [RIQ].	31.8 [20.51,1]	42.6 [25.8, 58.1]	0.093
Previous COVID-19, n (%)	1 (2.9)	2 (1.9)	0.162
COVID-19 vaccination, n (%)[a]	26 (78.8)	88 (83.3)	0.190
Seroconversion (>259 BAU/ml), n (%)[b]	11 (32.3)	53 (49.5)	0.123
Pre-exposure prophylaxis with tixagevimab/cilgavimab, n (%)	4 (11.8)	18 (16.8)	0.479
Hospitalization due to COVID-19, n (%)	34 (100%)	3 (2.8)	<0.001
Death, n (%)	5 (16.7)	0	<0.001

[a] According to the Ministry of Health vaccination schedule at the time of infection.
[b] Considered as humoral response (anti-S IgG > 259 BAU/ml) at the time of infection.

of these patients, it is possible that treatment at earlier stages of the disease would also have reduced the need for hospitalization and improved their evolution.

However, loss of efficacy of some of these drugs has recently been reported.[1,4,5] Moreover, the incidence of chronic kidney disease (CKD) among RT patients is high, and only molnupiravir and mABs are not contraindicated in patients with eGFR <30 ml/min/1.73 m^2.[1,6] But recent studies have questioned the efficacy of these two drugs, and both are already deauthorized in many countries.[4,5] Nirmatrelvir/ritonavir, in addition to being contraindicated in CKD stages greater than G3b, cause important drug-drug interactions that have limited its use in transplant recipients.[7] Finally, remdesivir has shown efficacy in the treatment of mild-moderate COVID-19, as we have also observed in this series.[8] Again, this drug is not recommended with eGFR <30 ml/min/1.73 m^2. However, initial experiences in patients with reduced eGFR, even on hemodialysis, show adequate efficacy and safety.[1,9]

Our study has limitations. It is a retrospective cohort, with the limitations inherent to this design. We do not have a control group, although we have analyzed, as a comparison group, all patients admitted for COVID-19 during the study period, who represent the population that developed severe disease among the RT patients in our area. Furthermore, this is a cohort with COVID-19 acquired during the omicron period, so the results cannot be extrapolated to possible new variants.

In conclusion, early treatment of COVID-19 in RT patients seems to reduce the risk of progression to severe COVID-19 and mortality. The lack of efficacy recently observed with some drugs and the contraindication of others raises questions about how to treat high-risk RT patients with CKD. Until new effective and safe therapies become available, we believe that it may be necessary to extend the experience with remdesivir to this group of RT patients with CKD, given the positive clinical results.

Financing

This research has not received specific support from public sector agencies, commercial sector or non-profit entities.

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https://doi.org/10.1016/j.nefroe.2024.06.003

Effect of early treatment with dapagliflozin on the natural history of chronic kidney disease

Efecto del inicio precoz de dapagliflozina en la evolución de la enfermedad renal crónica

Dear Editor,

In their recently published letter, Gippini and Prado[1] present an analysis of the renal benefits of earlier introduction of dapagliflozin. Although their idea is original, I think some remarks would be beneficial when drawing conclusions. First of all, the external validity of the findings is limited since the included studies are not the result of a systematic review, which make the results susceptible to evidence selection bias,[2] and since the basal characteristics of patients in each study are not presented, which makes the research question imprecise. Additionally, the calculations the authors present deserve some considerations.

First, an assumption is made that the difference between the decline rates of the estimated glomerular filtration rate (eGFR) in patients treated with dapagliflozin or placebo is constant through time. We do not have evidence supporting this assertion, but in the DAPA-CKD trial[3] the slopes of the eGFR vs time curves were different between the two groups. From the data presented in the letter,[1] as we will see, the eGFR decline ratio is different throughout the different values of eGFR reserve.

DOI of original article: https://doi.org/10.1016/j.nefro.2023.06.007.