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Use of remdesivir in kidney transplant recipients with SARS-CoV-2 Omicron infection

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Infection from the Omicron variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seems to be less severe in general population in comparison with the previous variants of concern.[1] However, in kidney transplant recipients (KTRs), Omicron continues to be a considerable threat[2] due to immunosuppression status and blunt response to vaccination.[3]

Clinical trials with remdesivir have demonstrated improved time to recovery in patients on oxygen with coronavirus disease 2019 (COVID-19).[4] In Spain, it was approved in September 2020 for the treatment of COVID-19 in patients with pneumonia, respiratory failure, and less than 8 days since symptoms' onset. Then, in consideration of the Phase 3 Randomized, Double-Blind Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Remdesivir (GS-5734™) Treatment of COVID-19 in an Outpatient Setting (PINETREE), patients with mild symptomatology and comorbidities were also considered to receive treatment with remdesivir because of its safety profile and the lower risk of hospitalization or death than placebo.[5]

Taking into consideration these data, the protocol of our institution (Hospital Clínic, Barcelona, Spain) was changed in November 2021 in order to include all patients with comorbidities (including solid-organ transplantation) to receive remdesivir, independent of the disease severity. The choice of administering remdesivir was also independent of kidney function, considering the different reports of safety in patients with estimated glomerular filtration rate (eGFR) <30 ml/min and/or acute kidney injury.[6,7] All patients who were asymptomatic and/or did not require hospitalization for the severity of COVID-19 were offered to receive remdesivir either at their home through the hospital-at-home (HaH) unit if they were living in the hospital area or by conventional hospitalization.

We conducted a retrospective cohort study on KTRs who contracted COVID-19 between November 1, 2021, and February 28, 2022. We assessed the impact of remdesivir on the primary outcome of severe COVID-19, defined as the need of high-flux nasal cannula, noninvasive mechanical ventilation, orotracheal intubation, or death at 30 days after symptoms' onset.

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Table 1 | Baseline characteristics of the studied population

	Total population (n = 98)	Not remdesivir (n = 41)	Remdesivir (n = 57)	*P* value
Age, yr (mean ± SD)	58.0 ± 16.3	55.7 ± 17.3	59.7 ± 15.4	0.371
Sex (% males)	52 (53.1)	22 (53.7)	30 (52.6)	1
Ethnicity, n (%)				0.425
• Caucasian	91 (92.9)	39 (95.1)	52 (91.2)	
• Hispanic	4 (4.1)	1 (2.4)	3 (5.3)	
• Asian	2 (2.0)	—	2 (3.5)	
• African	1 (1.0)	1 (2.4)	—	
Diabetes (% yes)	29 (29.6)	9 (22.0)	20 (35.1)	0.184
Body mass index, kg/m^2 (mean ± SD)	26.0 ± 4.9	26.7 ± 5.4	25.4 ± 4.6	
Current smoker (% yes)	7 (7.2)	3 (7.5)	4 (7.0)	1
Hypertension (% yes)	83 (84.7)	34 (82.9)	49 (86.0)	0.779
Ischemic heart disease (% yes)	14 (14.3)	6 (14.6)	8 (14.0)	1
Baseline eGFR, ml/min (mean ± SD)	40.5 ± 20.4	44.1 ± 21.9	37.8 ± 19.1	
• eGFR < 30 ml/min (% of patients)	35 (35.7)	13 (31.7)	22 (38.6)	0.527
Dialysis vintage, mo, median [IQR]	12 [0–35]	14 [0–23]	12 [0–36]	0.310
Time since transplantation, mo, median [IQR]	92 [31–162]	125 [29–164]	73 [32–159]	0.301
Type of transplant, n (%)				1
• Kidney	91 (92.8)	38 (92.5)	53 (93.0)	
• SPKT	7 (7.2)	3 (7.5)	4 (7.0)	
Previous transplant (% yes)	29 (29.6)	10 (24.4)	19 (33.3)	0.477
Baseline immunosuppression, n (%)				0.810
• TAC + MPA	66 (67.3)	27 (65.9)	39 (68.4)	
• TAC + mTORi	18 (18.4)	8 (19.5)	10 (17.5)	
• Corticosteroids (% yes)	83 (84.7)	32 (78.0)	51 (89.5)	0.212
• Dose (mean ± SD)	5.3 ± 4.7	4.7 ± 5.4	5.7 ± 4.2	
• Other	14 (14.3)	6 (14.4)	8 (14.0)	
Previous COVID-19 (% yes)	7 (7.1)	3 (7.3)	4 (7.0)	1
mRNA vaccination (≥2 doses) (% yes)	88 (89.8)	35 (85.4)	53 (93.0)	0.452
• 0 dose	1 (1.1)	0 (0)	1 (1.7)	
• 1 dose	2 (2.0)	2 (4.9)	0 (0)	
• 2 doses	15 (15.3)	4 (9.8)	11 (19.3)	
• 3 doses	70 (71.4)	28 (68.3)	42 (73.7)	
• 4 doses	3 (3.1)	3 (7.3)	0 (0)	
• Unknown	7 (7.1)	4 (9.8)	3 (5.3)	
Rejection during the last 6 months (% yes)	5 (5.1)	4 (9.8)	1 (1.8)	0.076

COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitors; SPKT, simultaneous pancreas-kidney transplantation; TAC, tacrolimus.

During this time frame, the Omicron variant in Spain was dominant,[1] and 98 patients followed up in our renal transplant unit developed COVID-19, of whom 57 (58.1%) received remdesivir and 41 (41.9%) did not. The latter category of patients included (i) patients who presented with disease onset >10 days or high–cycle threshold (CT) cycles >30, or both (n = 26); (ii) patients who were hospitalized in other hospitals with different protocols (n = 4); or (iii) patients who rejected hospitalization for living outside the hospital reference area (n = 11). Remdesivir was administered in a single dose of 200 mg, followed by 2 or 4 more daily doses of 100 mg, without renal function adjustment. A total of 5 patients (8.8%) received 3 doses, of whom 2 (40%) were asymptomatic. A total of 50 patients (87.7%) received 5 doses, of whom 46 (92%) were symptomatic. There were 2 isolated cases of patients who received 4 and 7 doses according to the severity of symptoms and the evolution of viral load. Median time between symptoms' start and administration of the first dose of the drug was 5 days (range, 3–8.5 days). Of the 57 patients who received remdesivir, 44 (77.2%) received it within the first week after symptoms' start, whereas the remaining 13 (22.8%) received it after.

In asymptomatic patients, doses of mycophenolic acid and/or mammalian target of rapamycin inhibitors were decreased. In symptomatic patients with pneumonia, mycophenolic acid and/or mammalian target of rapamycin inhibitors were withdrawn. In patients with significant symptomatology and/or need for oxygen therapy, also calcineurin inhibitors were withdrawn and immunosuppression was maintained with methylprednisolone or equivalent at a dose of at least 0.5 mg/kg/d.

Patients' characteristics are listed in Table 1. No major differences were observed with regard to baseline characteristics, chronic kidney disease and/or transplantation history, immunosuppression, and vaccination status between patients taking remdesivir or not. Almost all patients (84.6%) were

Table 2 | Clinical course and outcomes after administration or not of remdesivir of the studied population

	Total population (n = 98)	Not remdesivir (n = 41)	Remdesivir (n = 57)	*P* value
Clinical course (%)				0.308
• Asymptomatic (% yes)	13 (13.3)	7 (17.1)	6 (10.5)	
• Mild COVID-19 (% yes)	51 (52.0)	24 (58.6)	27 (47.4)	
• Moderate COVID-19 (% yes)	19 (19.4)	5 (12.2)	14 (24.6)	
• Severe COVID-19 (% yes)	15 (15.3)	5 (12.2)	10 (17.5)	
Hospitalization (including HaH) (% yes)	69 (70.4)	12 (29.3)	57 (100.0)	<0.001
Hospitalization (excluding HaH) (% yes)	54 (55.1)	12 (29.3)	42 (73.7)	0.001
Time from onset COVID-19 symptoms to onset remdesivir, d	—	—	5 (3–8.5)	
Other COVID-19 treatment, n (%)				
• Dexamethasone (% yes)	25 (25.5)	9 (22.0)	16 (28.1)	0.639
• Tocilizumab	15 (15.3)	5 (12.2)	10 (17.5)	0.575
• Baricitinib	7 (7.2)	1 (2.5)	6 (10.5)	0.234
Need of oxygen during hospital stay (% yes)	29 (29.6)	9 (22.0)	20 (35.1)	0.184
Pneumonia on chest X-ray (% yes)	31 (31.6)	10 (24.4)	21 (36.8)	0.271
Severe disease or death (% yes)	15 (15.3)	5 (12.2)	10 (17.5)	0.575
• Death (% yes)	7 (7.1)	2 (4.9)	5 (8.8)	0.460
Outcomes at 30 d after symptoms' onset, n (%)				0.380
• Discharged	87 (88.8)	38 (92.9)	49 (84.0)	
• Still hospitalized	5 (5.1)	1 (2.4)	4 (7.0)	
• Death	6 (6.1)	2 (4.9)	4 (7.0)	

COVID-19, coronavirus disease 2019; HaH, hospital-at-home.

vaccinated with at least 2 doses of an mRNA vaccine, the majority of them (71.4%) with the mRNA-1273 (Moderna) vaccine, whereas the other 13.2% with the BNT162b2 (Pfizer) vaccine. No patient received prophylactic monoclonal antibodies such as tixagevimab/cilgavimab (AZD7442, Evusheld; AstraZeneca).

Regarding COVID-19 presentation clinical course, no significant differences were observed in terms of pneumonia, need of oxygen, and use of other drugs, including dexamethasone, tocilizumab, and baricitinib.

A total of 13 of 98 (13.3%) patients were asymptomatic, 7 of whom received remdesivir and 6 did not. None of them developed severe COVID-19. Five cases developed COVID-19 during an unrelated hospitalization and all received remdesivir. At the time of receiving remdesivir, 12 patients (21.1%) were asymptomatic, 29 (50.9%) had mild COVID-19, 12 (21.1%) had moderate COVID-19, and 4 (7.0%) had severe COVID-19. Of the total number of patients who started with severe COVID-19 and received remdesivir,[4] only 1 patient died.

A total of 15 patients (26.3%) received remdesivir at their place of residence through the HaH unit, the majority of them (86.7%) being symptomatic; 2 of them (13.3%) were diagnosed with pneumonia on chest X-ray and 1 (6.7%) required oxygen. In 4 cases, patients were transferred from the emergency department after a short stay of a median (interquartile range) of 1 day (1–2 days), whereas in all the other 11 cases, HaH admission was direct from the outpatient department.

Fifteen patients developed severe COVID-19, defined as the need of high-flux nasal cannula, noninvasive mechanical ventilation, orotracheal intubation, or death (Table 2). In patients who received remdesivir during the first week after symptoms' start (n = 44), progression to severe COVID-19 or death was observed in 9.1% of cases. On the other hand, in patients who did not receive remdesivir or received it more than 1 week after symptoms' onset (n = 54), the primary outcome occurred in 20.4% of cases. At univariate logistic analysis (Supplementary Table S1), the factor that was most associated with the development of severe COVID-19 was the presence of pneumonia on chest X-ray at presentation with an odds ratio (OR) (95% confidence interval [CI]) of 54.35 (6.62–442.80, $P < 0.001$). The patient's age was also associated with the primary outcome, with an OR (95% CI) of 1.05 (1.00–1.09) per year increase ($P = 0.026$). The use of remdesivir was not associated with the outcome (OR [95% CI]: 1.53 [0.48–4.87], $P = 0.470$). However, when taking into account its early use (≤7 days since symptoms' onset), it was associated with protection from the outcome in hospitalized patients, either including patients admitted to HaH (OR [95% CI]: 0.13 [0.03–0.47], $P = 0.002$) or not (OR [95% CI]: 0.15 [0.03–0.64], $P = 0.010$). In the time-to-event analysis, early use of remdesivir was still associated with a more favorable outcome in comparison with late or null administration only in hospitalized patients (Figure 1).

In patients receiving remdesivir, kidney function did not worsen at hospital discharge (baseline eGFR [mean ± SD]: 39.0 ± 18.7 ml/min, at discharge [mean ± SD]: 41.8 ± 20.9 ml/min, $P = 0.189$), also in patients with baseline eGFR <30 ml/min (baseline 20.4 ± 4.5 ml/min, at discharge 28.4 ± 17.3 ml/min, $P = 0.078$). Three patients in the remdesivir group started chronic hemodialysis during their hospital stay, as their kidney function was already deteriorated before admission (baseline eGFR [median (IQR)]: 8 [7–13] ml/min). Two of them started hemodialysis before receiving the drug and 1 after receiving it.

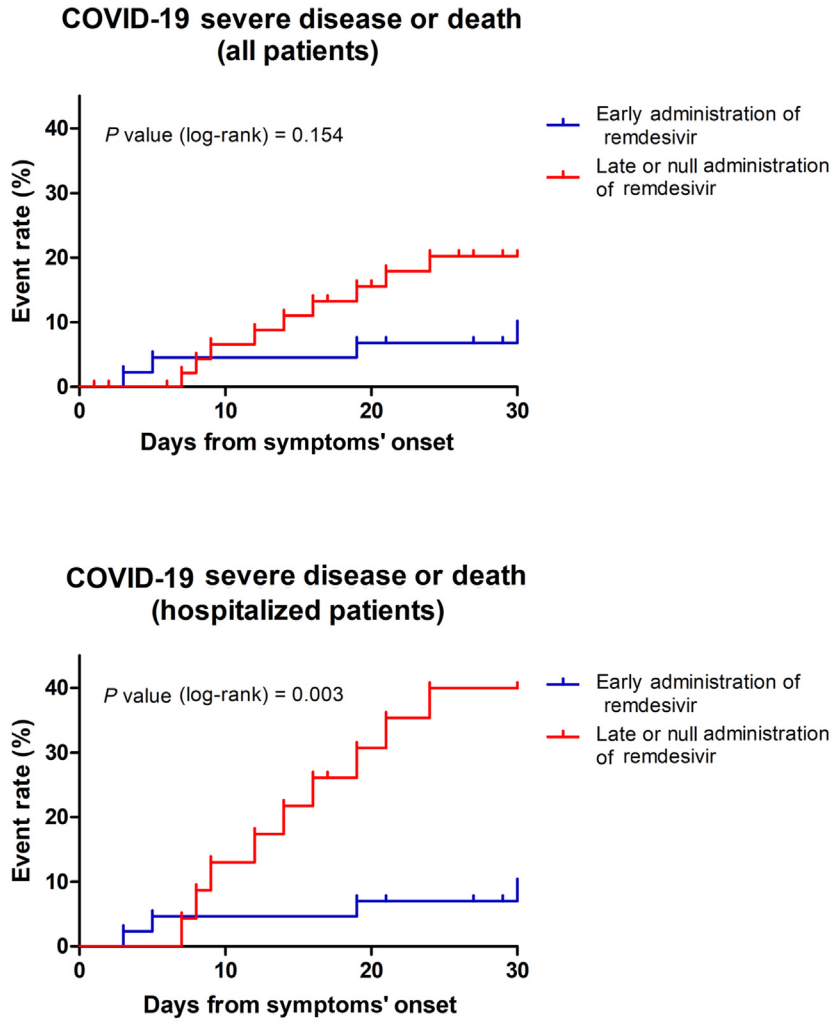

Figure 1 | Time-to-event analysis (Kaplan-Meier) for patients receiving remdesivir as early administration (≤7 days from symptoms' start, blue line) or for patients with late or null administration (red line). The upper panel shows results for all patients' population, whereas the lower panel shows results only for hospitalized patients (including hospital at home).

Patients who received remdesivir in the hospital had a median (interquartile range) length of stay of 8 (5–17) days, not significantly different from the control group: 14 (6–19) days, $P = 0.477$. Considering also patients who were transferred to the HaH unit, the total length of stay (HaH + hospital) lowered to 7 (5–13.75) days in patients taking remdesivir, not significantly different from patients not taking it ($P = 0.226$).

In conclusion, in our cohort of patients who received remdesivir for COVID-19, we observed protection from severe disease only in hospitalized patients with early administration of the drug (≤7 days within symptoms' onset). This is coherent with data in general population that indicate that the drug is effective if given properly during the viremic phase of the disease.[5] In terms of safety, our data also suggest that it can be administered safely in KTRs also with eGFR <30 ml/min.

The limitations of our study include its retrospective nature and a small sample size in order to obtain more solid conclusions. Patients not treated with remdesivir were not hospitalized in more than two-thirds of cases, probably reflecting less severe cases of COVID-19. Conversely, patients who received remdesivir had to be admitted to receive the medication, which increased the number of admissions in this group. This may highlight an inherent selection bias for which patients at lower risk of complications from COVID-19 did not receive remdesivir. This is also highlighted by the observation that in the whole population, the time of remdesivir initiation was not associated with the primary outcome. In terms of severe disease, another bias could be a lower threshold for receiving remdesivir in sicker patients, linked to a higher likelihood of developing severe disease in this group. However, in both cases, this could have theoretically skewed the results in favor of the not-remdesivir group and not the contrary.

On the other hand, the control group was well matched in terms of all the other baseline parameters and developed COVID-19 during the same epidemic wave. This adds value to the present work, because so far reports have been focused

only on the safety of remdesivir in KTRs and no control groups have been reported. Other strategies that may be employed against COVID-19 in KTRs include passive immunization with monoclonal antibodies active against the Omicron variant (sotrovimab)[2] and further boosts of immunization with mRNA or heterologous vaccines.

DISCLOSURE

All the authors declared no competing interests.

DATA STATEMENT

The data that support the findings of this study are available on reasonable request addressed to the corresponding author.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Methods.

Table S1. Univariable analysis on factors associated with severe coronavirus disease 2019 (COVID-19), defined as the need of high-flux nasal cannula, noninvasive mechanical ventilation, orotracheal intubation, or death at 30 days after symptoms' onset. Estimation of vaccine responsiveness was assessed by odds ratio (OR) and their 95% confidence intervals (95% CIs) by means of logistic regression analysis.

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