

Remdesivir in Solid Organ Recipients for COVID-19 Pneumonia

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ABSTRACT

Solid organ transplant (SOT) recipients represent a vulnerable patient population and are of high risk for airborne viral infections, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). Treatment of COVID-19 is still challenging, as no proven therapeutic regimen is available for immunocompromised patients. Our aim was to evaluate the efficacy and safety of remdesivir (RDV) therapy in infected hospitalized SOT patients. All transplanted recipients (N = 25; lung: 19; kidney: 3, liver: 2, heart: 1) who needed hospital care were reviewed in the time period between September 2020 and May 2021 out of the 945 patients treated at the Department. Case control matched patients receiving RDV (all in need of supplementary oxygen) and standard of care (SOC) were included as controls. Among the 25 SOT patients (female: male = 11:14; average age = 53.2 ± 12.7 years), 15 received RDV medication (RDV-TX), and in 10 cases SOC treatment was used (SOC-TX). Significantly worse clinical score was noted in RDV patients compared with RDV-TX; however, transfer to a higher intensity care unit as well as 60-day survival of RDV-TX patients were significantly worse. All SOT fatalities within 60 days of follow-up were lung transplant recipients (6 out of 19 lung transplant patients). No adverse events were noted related to RDV therapy. In SOT patients, especially lung transplant recipients, with severe COVID-19 needing supplementary oxygen, RDV treatment was safe; however, outcome was significantly worse as compared with nontransplanted individuals with initially worse clinical parameters.

SOLID organ transplant (SOT) patients represent a vulnerable patient population for airborne viral infections, including the new coronavirus disease 2019 (COVID-19). As recipients receive high doses of immunosuppressive medications, they might be at a high risk of severe illness from COVID-19 and increased mortality [1]. On the other hand, immunosuppressants may mask or delay cytokine storm and influence patient management, balancing the patients' survival toward the values observed in nontransplanted patients [2–4]. Studies have reported conflicting data on whether SOT recipients have higher risk of more severe illness or increased mortality, compared with non-SOT recipients [2–5]. Furthermore, we have limited knowledge of the safety and efficacy of targeted therapies for COVID-19 in the SOT recipients [6].

Remdesivir (RDV) is a direct-acting antiviral agent, a nucleotide analog pro-drug, used in the treatment for patients with severe COVID-19. The Adaptive Covid-19 Treatment Trial has confirmed superiority to placebo in shortening time to recovery in hospitalized adults in need of supplementary oxygen therapy

[7]. Another study suggests that RDV has no significant effect on mortality; however, it reduces the risk of mechanical ventilation and serious complications, and improves the recovery percentage as well [8]. Few data are available about efficacy and safety of RDV in the treatment of severe COVID-19 in SOT patients [4,6].

MATERIALS AND METHODS

Patients admitted to the COVID Units of the Department of Pulmonology Semmelweis University between September 2020 and May 2021 were evaluated (N = 945). During this period all SOT patients were analyzed, including 19 lung transplant and 6 other organ SOT patients. Anthropometric data, time since transplant and indications for

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transplant, length of hospital stay and 60-days survival, comorbidities (Charlson comorbidity score), National Early Warning Score (determinates the degree of the illness of the patient), outcomes/discharge destinations, and additional therapy (oxygen supplementary and immunosuppressive treatment) were analyzed. Patients were divided according RDV treatment (RDV-TX) and standard of care only treatment (SOC-TX), and case control patients without grafts were included (RDV and SOC, respectively). Case-control analyzing was made according to sex, age, and admission day at hospital. Statistical analysis was made by Student *t* test and χ^2 test, and $P < .05$ was considered statistically significant.

RESULTS

Patient characteristics are summarized in Table 1. No differences in age and sex distribution were noted. RDV patients presented with significantly worse baseline National Early Warning Score as compared with RDV-TX. All patients treated with RDV needed supplementary oxygen due to lung involvement. Only one SOC-TX patient was treated shortly with oxygen who had deteriorated so quickly that intensive care transfer preceded the start of planned RDV treatment. Hospital length of stay was significantly longer in RDV-TX as compared with RDV patients. Survival assessed at 60-days was significantly

worse in RDV-TX patients, and all recipients who died ($n = 6$) were lung transplant patients. None of the RDV or RDV-TX patients had therapy-related adverse events.

DISCUSSION

Our data indicate that RDV is safe in SOT recipients; however, severe COVID-19 cases in need of supplementary oxygen show high mortality despite antiviral treatment. Previous studies have reported differences in mortality rate, which varies from 2.5% to 37.0 % among SOT patients, and mostly the data indicates a not significant difference between the SOT and normal/control population [2-4,6,9]. At the beginning of the pandemic, limited information was available about outcomes in SOT recipients treated with more recent therapies such as RDV, dexamethasone, and convalescent plasma [6]. Treatment mostly included conditional recommendations and exemptions for use by regulatory bodies including the European Medical Agency or Hungarian National Institution of Pharmacy and Nutrition [10].

Treatment options should be chosen carefully in the SOT patient population. Data are conflicting whether immunosuppressants influence the outcome or severity of COVID-19 [2]. Although the dose reduction of immunosuppressive drugs

Table 1. Patient Characteristics and Outcome

	All Patients	RDV-TX	RDV	SOC-TX	SOC
N	100	15	45	10	30
Age (y)		55.7 $\pm$ 12.3	56.8 $\pm$ 12.0	49.6 $\pm$ 13.1	51.1 $\pm$ 12.0
Sex n (%)					
Female	44 (44)	7 (47)	21 (47)	4 (40)	12 (40)
Male	56 (56)	8 (53)	24 (53)	6 (60)	18 (60)
Time since transplant (y)					
<1 y		5	-	4	-
>1 y		10	-	6	-
Indications for transplant n (%)					
COPD (lung)	10 (40)	7 (47)	-	3 (30)	-
Interstitial lung disease (lung)	4 (16)	4 (26)	-	0 (0)	-
Cystic fibrosis (lung)	3 (12)	2 (13)	-	1 (10)	-
Other (lung)	2 (8)	0 (0)	-	2 (20)	-
Kidney failure (kidney)	3 (12)	1 (7)	-	2 (20)	-
Cirrhosis hepatitis (liver)	2 (8)	1 (7)	-	1 (10)	-
Heart failure (heart)	1 (4)	0 (0)	-	1 (10)	-
Length of hospital stay (d)		17.8 $\pm$ 15.0*	11.1 $\pm$ 7.5	11.7 $\pm$ 7.4	6.4 $\pm$ 5.5
60-days survival n (%)		9 (60)* [‡]	42 (93)	10 (100)	26 (87)
Charlson comorbidity score (0-8)		4.4 $\pm$ 2.1	3.2 $\pm$ 2.0	3.0 $\pm$ 1.4	2.1 $\pm$ 2.1
Baseline NEWS		4.6 $\pm$ 2.6*	7.0 $\pm$ 2.3 [‡]	4.2 $\pm$ 2.3	4.3 $\pm$ 4.1
Outcomes n (%)					
ICU/noninvasive ventilation therapy/death	22 (22)	7 (47)	8 (18)	1 (10)	6 (20)
Home/other hospital	78 (78)	8 (53)*	37 (82)	9 (90)	24 (80)
Additional therapy n (%)					
Oxygen	61 (61)	15 (100)	45 (100)	1 (10)	0 (0)
Steroid	97 (97)	15 (100)	45 (100)	9 (90)	30 (100)
Tacrolimus	24 (24)	15 (100)	-	9 (90)	-

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NEWS, National Early Warning Score; RDV, remdesivir; SOC, standard of care; TX, transplanted patient.

* $P < .05$ vs RDV.

[†] $P < .05$ vs SOC.

[‡] $P < .05$ vs SOC-TX.

might increase the risk of transplant rejection, it is recommended and widely practiced in transplant recipients during COVID-19 infection [2,3,9]. In all of our SOT patients mycophenolate was temporarily ceased; however, there is no evidence-based protocol or consensus about the exact details on immunosuppression therapy, but it is mostly agreed that continuing a decreased dose of immunosuppressants may provide protection against a severe inflammatory phase [6].

CONCLUSIONS

Lung transplant patients had a high 60-day mortality, confirming these SOT patients are even more vulnerable to COVID-19 pneumonia as compared with other graft recipients. RDV therapy was safe in all SOT patients, and further therapeutic protocols are needed to protect grafts and patients from SARS-Cov2—induced severe organ damage and COVID-19 death.

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