



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



ELSEVIER

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

Early remdesivir to prevent severe COVID-19 in recipients of solid organ transplant: a real-life study from Northern Italy

Marta Colaneri^{1,*}, Nicolò Amarasinghe¹, Leonardo Rezzonico¹, Teresa Chiara Pieri¹, Emilio Segalini¹, Margherita Sambo¹, Silvia Roda¹, Federica Meloni², Marilena Gregorini³, Teresa Rampino³, Stefano Pelenghi⁴, Alessandra Ricciardi¹, Raffaele Bruno⁵

¹ Division of Infectious Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

² Division of Pneumology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

³ Division of Nephrology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

⁴ Division of Cardiac Surgery, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

⁵ Department of Medical, Surgical, Diagnostic and Paediatric Science, University of Pavia, Italy

ARTICLE INFO

Article history:

Received 8 April 2022

Revised 28 April 2022

Accepted 1 May 2022

Keywords:

COVID-19

Solid organ transplant recipients

3-day course remdesivir

ABSTRACT

Objectives: The effectiveness of a 3-day course of remdesivir to prevent severe disease in patients with COVID-19 who received solid organ transplant (SOT) is unknown. We wanted to study the efficacy of this therapeutic option in patients with COVID-19 who received SOT in preventing both hospitalizations for outpatients and clinical worsening due to COVID-19 for those already hospitalized for other reasons.

Methods: This is a single-center, retrospective, observational study conducted in the Fondazione IRCCS Policlinico San Matteo of Pavia, Northern Italy. We extracted all the data of patients with COVID-19 receiving SOT who received and did not receive pre-emptive remdesivir between December 23, 2021, and February 26, 2022. We used a Cox proportional hazard model to assess whether receiving pre-emptive remdesivir was associated with lower rates of hospitalization.

Results: A total of 24 patients who received SOT were identified. Among these, seven patients (29, 1%) received pre-emptive remdesivir, whereas 17 (70, 9%) patients did not. Receiving remdesivir significantly reduced the hospitalization rate in outpatients who received SOT and the clinical worsening of the condition of already hospitalized patients who received SOT (hazard ratio 0.05; confidence interval [0.00–0.65], P -value = 0.01).

Conclusion: In our cohort of patients infected with SARS-CoV-2 who received SOT, pre-emptive remdesivir was effective in reducing the hospitalization rate due to COVID-19 and in preventing the clinical worsening of the condition of patients who received SOT who were hospitalized for reasons other than COVID-19.

© 2022 Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Introduction

COVID-19 remains a life-threatening disease for recipients of solid organ transplant (SOT) who might not mount an adequate protective response to vaccination (Sait et al., 2022). With this in mind, it is extremely relevant to deal with the recent SARS-CoV-2 infection in these patients, starting with treatments which may prevent the COVID-19 progression (National Institutes of Health, 2022b).

Remdesivir, a nucleotide inhibitor of SARS-CoV-2 RNA-dependent RNA polymerase, has been recently proposed in a 3-day course to prevent hospitalization; however, patients who are severely immunocompromised, such as patients who received SOT, have been underrepresented (Gottlieb et al., 2022). We aimed to investigate the real-life impact of pre-emptive administration of a 3-day course of remdesivir in reducing hospitalization due to COVID-19 in patients who received SOT.

Materials and methods

Our hospital, Fondazione IRCCS Policlinico San Matteo (PSM) of Pavia, is a COVID-19 referral hub in Northern Italy.

* Corresponding author: Marta Colaneri, MD, Infectious Diseases I Unit, IRCCS San Matteo, Pavia, Italy, ORCID 0000-0002-5939-9576.

E-mail address: m.colaneri@smatteo.pv.it (M. Colaneri).

Table 1
Demographic and clinical characteristics.

Variable		Whole sample (n=24)	Remdesivir(n=7)	No Remdesivir (n=17)	P-value
Sex, n (%)	Male	18 (75%)	5 (71.4)	13 (76.5)	0.10
	Female	6 (25%)	2 (28.6)	4 (23.5)	
Age (years), median [IQR]		57 [51.8, 64.8]	60 [52.0, 66.5]	55 [51, 64]	0.75
Vaccination doses, n (%)^a	0	0 (0.0)	0 (0.0)	0 (0.0)	0.58
	1	0 (0.0)	0 (0.0)	0 (0.0)	
	2	1 (5.0)	0 (0.0)	1 (6.2)	
	3	19 (95.0)	4 (100.0)	15 (93.8)	
SOT type, n (%)	Kidney	19 (79.2)	5 (71.4)	14 (82.4)	0.10
	Liver	2 (8.3)	0 (0.0)	2 (11.8)	
	Lung	1 (4.2)	1 (14.3)	0 (0.0)	
	Heart	2 (8.3)	1 (14.3)	1 (5.9)	
Length of transplantation (days), median [IQR]		2051 [642.2–3425.0]	2555 [1297–3845]	705 [94.5–1465.5]	
Immunosuppressive therapy					
Cyclosporin, n (%)		5 (20.8)	2 (28.6)	3 (17.6)	0.96
Azathioprine, n (%)		1 (4.2)	1 (14.3)	0 (0.0)	0.63
Mycophenolate, n (%)		15 (62.5)	4 (57.1)	11 (64.7)	1.00
Steroid, n (%)		12 (50.0)	4 (57.1)	8 (47.1)	1.00
Steroid dosage (mg), mean (SD) ^b		5.5 (8)	6.8 (9.2)	5 (7.7)	0.63
Everolimus, n (%)		6 (25.0)	3 (42.9)	3 (17.6)	0.43
Tacrolimus, n (%)		17 (70.8)	5 (71.4)	12 (70.6)	1.00
Sirolimus, n (%)		1 (4.3)	0 (0.0)	1 (6.2)	1.00
Positive IgG antispikes SARS-CoV-2, n (%)^c		16 (66.7)	6 (85.7)	10 (58.8)	0.42
Comorbidities					
Neoplasm, n (%)		1 (4.2)	0 (0.0)	1 (5.9)	1.00
CKD, n (%)		20 (83.3)	5 (71.4)	15 (88.2)	0.68
CVD, n (%)		9 (37.5)	2 (28.6)	7 (41.2)	0.90
HTN, n (%)		21 (87.5)	6 (85.7)	15 (88.2)	1.00
DM, n (%)		4 (16.7)	2 (28.6)	2 (11.8)	0.68
Lung disease, n (%)		4 (16.7)	2 (28.6)	2 (11.8)	0.68
Positive HCV antibodies, n (%)		2 (8.3)	1 (14.3)	1 (5.9)	1.00
Obesity, n (%)		4 (16.7)	1 (14.3)	3 (17.6)	1.00
Total comorbidity, mean (SD)		2.7 (1)	2.7 (1.3)	2.7 (0.8)	0.98
Smoke, n (%)		4 (16.7)	1 (14.3)	3 (17.6)	1.00
Symptoms on onset					
Nonasymptomatic, n (%)		20 (100.0)	7 (100.0)	13 (100.0)	0.18
Fever, n (%)		7 (35.0)	2 (28.6)	5 (38.5)	1.00
Cough, n (%)		10 (50.0)	3 (42.9)	7 (53.8)	1.00
Pharyngodynia, n (%)		7 (35.0)	3 (42.9)	4 (30.8)	0.96
Dyspnea, n (%)		5 (25.0)	1 (14.3)	4 (30.8)	0.78
Asthenia, n (%)		7 (38.9)	4 (57.1)	3 (27.3)	0.44
Hospital admission or COVID-19 worsening, n (%)		9 (37.5)	0 (0.0)	9 (52.9)	0.04
ICU admission, n (%)		1 (4.2)	0 (0.0)	1 (5.9)	1.00

Note: BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; HCV, hepatitis C virus; ICU, intensive care unit; IQR, interquartile range; SOT, solid organ transplant; Obesity considered as BMI >30 kg/m².

^a The information regarding the vaccination status was available for 20/24 patients.

^b Dosage in mg refers to prednisone dose.

^c IgG antitrimeric SARS-CoV-2 spike protein was considered positive when ≥ 50 AU/ml.

From December 2021, one of the PSM Infectious Diseases outpatient clinics has been allocated to the pre-emptive care of outpatients with COVID-19.

Specifically, an infectious disease specialist was in charge of receiving daily emails from general practitioners and other specialists who notified the cases of high-risk outpatients with SARS-CoV-2 or inpatients admitted for reasons other than COVID-19. For each patient, the most appropriate therapy was chosen from among sotrovimab, remdesivir, molnupiravir, and ritonavir-boosted nirmatrelvir.

The medical records of patients with COVID-19 receiving SOT who were consequently evaluated between December 23, 2021, and February 27, 2022, for pre-emptive therapy in our clinic were reviewed, and data were abstracted on standardized data collection forms.

According to the Agenzia Italiana del Farmaco (AIFA) (AIFA, 2022), the administration of 3-day remdesivir was not recommended in patients with eGFR <30 ml/min and those with symptom onset >7 days. We also excluded patients who received pre-emptive treatments other than remdesivir, allowing a direct comparison between patients who did and did not receive the drug.

Outcomes

The primary outcome was the impact of a 3-day course of remdesivir in preventing hospitalization due to COVID-19 in outpatients who received SOT at day 28 after the first positive nasal swab and the progression of COVID-19 in those already hospitalized for other reasons according to the National Institute of Health Guidelines (National Institutes of Health, 2022a).

The secondary outcome was the evaluation of remdesivir impact on the median duration of negativization of the nasopharyngeal SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) swab.

Statistics

Data for continuous variables are presented as medians and interquartile ranges (IQRs). Categorical variables are presented as frequencies and percentages. Comparisons between the remdesivir and nonremdesivir groups of patients who received SOT were performed using chi-square tests and Mann-Whitney *U* tests.

The log-rank test was used to estimate the difference between the Kaplan and Meier 28-day hospitalization curves of patients

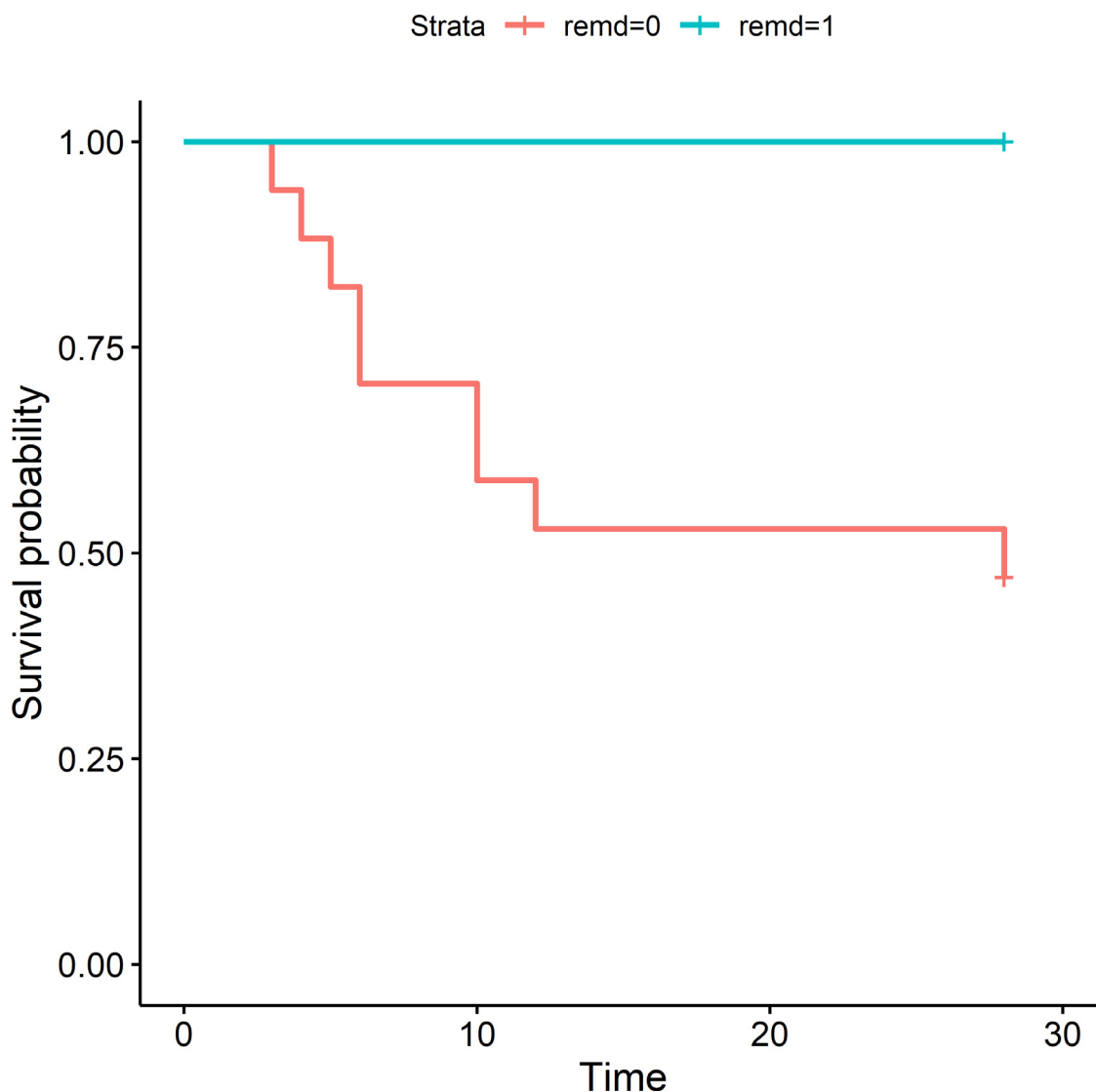


Figure 1. Cox regression model shows reduced hospital admission at 28 days from the positivization of reverse transcription polymerase chain reaction (RT-PCR) nasal swab for SARS-CoV-2.

who received and did not receive pre-emptive therapy. Then, a Cox proportional hazard model was used, controlling for sex, age, number of underlying comorbidities, antispikes IgG antibodies, and length of time from transplantation to SARS-CoV-2 infection. The results are reported as hazard ratios (HRs) and 95% confidence intervals (CIs). Statistical analyses were conducted with R vs 4.1.2.

Results

Data were extracted from 24 patients. Demographic and clinical features are reported in Table 1.

With regard to remdesivir pre-emptive therapy, seven patients (29, 1%) were treated with this drug, whereas 17 (70, 9%) patients were not. Among those who were not treated with remdesivir, five had CKD (egfr < 30 ml/min, but none were in chronic dialysis replacement), whereas 12 were asymptomatic at the time of COVID-19 diagnosis.

Among the 24 patients, 8 were already hospitalized for non-COVID-19 related reasons. Among them, only one patient was treated with the 3-day remdesivir course, and the patient had no clinical worsening due to COVID-19. None of the patients required mechanical ventilation, and one patient died.

For outpatients, patients who received early remdesivir were not hospitalized and had no COVID-19 worsening.

Treatment with early remdesivir significantly reduced hospital admission at 28 days from the first positive nasopharyngeal RT-PCR swab for SARS-CoV-2 in the Kaplan-Meier curve (Figure 1).

After accounting for gender, age, comorbidities count, and positivity of IgG antispikes SARS-CoV-2, the multivariable Cox proportional hazard regression model showed that remdesivir administration had a significant effect on reducing the hospitalization rate and progression of COVID-19 (aHR 0.05; CI [0.00–0.65], P-value = 0.01).

No differences in the median duration of negativization of the nasopharyngeal SARS-CoV-2 RT-PCR swab between the two groups was found (P-value = 0.86).

Discussion

Our results showed a significant impact of an early 3-day course of remdesivir in preventing COVID-19-related hospitalization and disease progression in patients who received SOT with moderate symptoms of SARS-CoV-2 infection.

Although having no impact on the survival of patients with COVID-19 (Beigel John et al., 2020; Siemieniuk et al., 2020), remdesivir had a benefit when treatment was initiated in the early stage of SARS-CoV-2 infection (Heil and Kottlilil, 2022; Wilt et al., 2021).

Recently, Gottlieb et al demonstrated the efficacy of an early 3-day course of remdesivir in preventing COVID-19-related hospitalization among outpatients with mild to moderate COVID-19 and risk for progression to severe disease (Gottlieb et al., 2022). However, patients receiving SOT who need special consideration and effective early treatments owing to their scarce immune response to COVID-19 vaccination were underrepresented.

Due to the possible adaptive mutations of variants in the spike protein, which might result in escape phenomena to monoclonal antibodies, antiviral agents remain a more valuable choice.

Although with the small sample size and the retrospective nature of the study, we can be satisfied with the first report on these patients who were, are, and possibly will be one of the most affected by SARS-CoV-2.

Ethical approval statement

This study is a retrospective analysis of the SMAtteo Covid 19 Registry (SMACORE) cohort, approved by our institutional review board (n.Prot 20200046877), which included patients with a diagnosis of COVID-19 referred to our hospital, PSM of Pavia.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

The authors have no competing interests to declare.

References

- AIFA, AIFA statement. https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_004796_048854_RCP.pdf&sys=m0b113, 2022. (accessed 4 March 2022).
- Beigel John H, Tomashek Kay M, Dodd LE, et al. Remdesivir for the treatment of Covid-19 – final report. *N Engl J Med* 2020;383:1813–26.
- Gottlieb RL, Vaca CE, Paredes R, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med* 2022;386:305–15.
- Heil EL, Kottlilil S. The goldilocks time for remdesivir – is any indication Just Right? *N Engl J Med* 2022;386:385–7.
- National Institutes of Health, COVID-19 treatment guidelines: clinical spectrum of SARS-CoV-2 infection. <https://www.covid19treatmentguidelines.nih.gov/overview/clinicalspectrum/?msclkid=f5a68397b58d11ecac33ca54b94a2a00>, 2022a. (accessed 4 March 2022).
- National Institutes of Health. Statement on patient prioritization for outpatient therapies. COVID-19 Treatment Guidelines [internet]; 2022b (accessed 4 March 2022) <https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/>.
- Sait AS, Chiang TP-Y, Marr KA, et al. Outcomes of SOT recipients with COVID-19 in different eras of COVID-19 therapeutics. *Transplant Direct* 2022;8:e1268.
- Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Kum E, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *BMJ* 2020;370:m2980.
- Wilt TJ, Kaka AS, MacDonald R, Greer N, Obley A, Duan-Porter W. Remdesivir for adults with COVID-19: a living systematic review for American College of Physicians practice points. *Ann Intern Med* 2021;174:209–20.