New Microbiologica, 45, 4, 304-307, 2022, ISSN 1121-7138

FULL PAPER

Early 3-day course of remdesivir to prevent progression to severe Covid-19 in high-risk patients with hospital-acquired SARS-CoV-2 infection: preliminary results from two Italian outbreaks

Simone Meini[1], Irene Bracalente[1], Giulia Bontempo[2], Benedetta Longo[1], Maria De Martino[3], Carlo Tascini[2]

[1]*Internal Medicine Unit, Felice Lotti Hospital, Pontedera, Azienda USL Toscana Nord-Ovest, Italy;*
[2]*Infectious Disease Unit, Department of Medicine, University of Udine, Italy;*
[3]*Division of Medical Statistics, Department of Medicine (DAME), University of Udine, Italy*

SUMMARY

In multimorbid, unvaccinated and non-hospitalized patients, early administration of remdesivir, nirmatrelvir/ritonavir and molnupiravir was effective in reducing the risk of hospitalization or death from any cause. Similar data are lacking with regard to patients already hospitalized and who acquire in-hospital SARS-CoV-2 infection.

We conducted a retrospective study during two outbreaks of SARS-CoV-2 infections involving 90 inpatients already hospitalized for medical or surgical conditions, in order to assess the effectiveness of early administration of remdesivir. Forty-seven cases were treated with a 3-day course of remdesivir (200 mg on day 1 and 100 mg on days 2 and 3) within a median time of 1.4 day from testing positive, and were compared to a matched case-control cohort of 43 untreated patients; matching was based on age, sex, vaccination status, previous symptomatic infections by SARS-CoV-2, reasons for hospitalization (no significant differences).

No case presented adverse events to remdesivir or death from COVID-19. No significant difference in overall in-hospital mortality was observed in cases compared to controls (17% *vs* 16.3%, p=0.925), but progression to severe pneumonia, although the difference was still not significant, showed an evident trend of a better outcome (8.5% *vs* 16.3%, p=0.261). Moreover, cases had a median discharge delay of 3 days (p=0.008).

Received July 7, 2022 *Accepted* November 11, 2022

INTRODUCTION

After two years, despite effective vaccination campaigns, the COVID-19 pandemic continues to challenge our healthcare systems, and several new SARS-CoV-2 variants of concern have appeared. Elderly and multimorbid patients, representing the majority of hospitalized patients, have an increased risk of progression to severe disease, disability and death. Outbreaks of SARS-CoV-2 infection in institutional settings, such as hospitals and long-term care facilities, have been an issue since the start of the pandemic: effective treatments promptly administered at a suitable disease stage could save many lives (Dölken *et al*., 2021).

Key words:
Remdesivir; early treatment; COVID-19; SARS-CoV-2; nosocomial infection.

Corresponding author:
Simone Meini, MD
E-mail: simonemeini2@gmail.com

Phase 3 trials showed that remdesivir, administered to adult patients hospitalized for SARS-CoV-2-related pneumonia, both as 10-day (Beigel *et al.*, 2020) and 5-day course (Goldman *et al*., 2020), shortens the recovery time and allows early clinical improvement. Remdesivir, compared to placebo, reduced the likelihoods of requiring high-flow supplemental oxygen and invasive mechanical ventilation, as well as the risk of 14-day mortality (Angamo *et al*., 2022).

Since the highest viral load and infectivity of SARS-CoV-2 are observed within the first 5 days from symptom onset (Wölfel *et al*., 2020), early administration of remdesivir seems crucial. Recently, a 3-day course within 7 days from symptom onset proved effective in reducing the risk of hospitalization or death from any cause among unvaccinated outpatients at high risk for COVID-19 progression due to their comorbidities (Gottlieb *et al.*, 2022). Likewise, both oral nirmatrelvir/ritonavir and molnupiravir, administered within 5 days from symptom onset to high-risk, unvaccinated and non-hospitalized adult patients, showed a reduction of COVID-19-related

hospitalization or 28-day all-cause mortality (Hammond *et al.*, 2022, Jayk Bernal *et al.*, 2022).
Similar data concerning early administration of antivirals in patients hospitalized due to other diagnoses and who acquire in-hospital SARS-CoV-2 infection is lacking. Indeed, this population is at high risk of disease progression toward severe forms of Covid-19, due to both acute illness and severity of the underlying cause of hospitalization and frequent comorbidities. Evidence on the effectiveness of an early antiviral treatment in this setting is warranted.
Herein, we report the results of a retrospective study conducted in two Italian hospitals during two outbreaks of SARS-CoV-2 infections occurring among inpatients already hospitalized for medical or surgical conditions, in order to assess the effectiveness of early administration of remdesivir.

MATERIALS AND METHODS

Study design

We retrospectively evaluated 90 consecutive inpatients who initially tested negative to SARS-CoV-2 when hospitalized for several medical or surgical conditions, and subsequently acquired in-hospital SARS-CoV-2 infection. All infections were confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) on nasopharyngeal swabs.
All patients presenting risk factors described by Gottlieb *et al.* (Gottlieb *et al.*, 2022) were deemed at high risk of progression to severe Covid-19 and were considered potentially suitable for antiviral therapy. Eligible patients included individuals aged sixty and above, as well as patients aged 12 years or above with at least one preexisting risk factor, such as hypertension, cardio-cerebrovascular disease, diabetes, obesity, chronic mild-moderate kidney disease, chronic lung disease, ongoing active cancer, and immune-compromised patients (Gottlieb *et al.*, 2022).
Specific contraindications to the treatment were: eGFR <30 ml/min, liver failure, body weight less than 40 kg. Remdesivir was not administered if more than 5 days from onset of symptoms or testing positive had passed, or in case of denied consent to the treatment. All patients provided their informed consent for the treatment.
Overall, a total of 47 patients (defined as cases) underwent a 3-day course of remdesivir (200 mg on day 1 and 100 mg on days 2 and 3) as soon as they tested positive, upon routine screening assessments or after incidental close contact with a known-positive patient, or due to onset of new symptoms.
The 47 patients treated with remdesivir were compared to a matched case-control cohort consisting of 43 patients who tested positive to SARS-CoV-2 in the same frame time and who were not treated due to denied consent, or who were not eligible due to the specific contraindications above mentioned. Matching was performed according to age, sex, vaccination status, previous symptomatic SARS-CoV-2 infection and reason for hospitalization, but, due to the above reasons, the two groups may not be fully comparable.

Setting

The two outbreaks, both lasting about 30 days, occurred in January-February 2022 and involved both the medical and surgical departments of "Santa Maria della Misericordia" Hospital of Udine (UH) and the medical area of "Felice Lotti" Hospital of Pontedera, Pisa (PH). UH is a university hospital with approximately 700 beds, including 188 beds in medical and 204 in non-Covid surgical wards, admitting 2110 patients in the referral period. PH is a secondary hospital with approximately 260 beds, including during the study period 56 medical beds dedicated to management of non-Covid patients, admitting 98 patients in the referral period, and 24 medical beds dedicated to management of Covid patients.

Outcomes

The main outcomes were: progression to severe pneumonia requiring supplemental oxygen or non-invasive ventilation; overall in-hospital mortality; length of stay, and discharge delay due to SARS-CoV-2 infection.

Statistical analysis

Descriptive statistics for categorical variables are presented as numbers (percent) and for continuous variables as mean ± standard deviation (SD) or median (interquartile range (IQR)). Normality was assessed using Shapiro-Wilk test. Comparisons between categorical variables were performed using the Chi-square or Exact Fisher test, as appropriate. For continuous variables, comparisons were made by using the t-test or Mann-Whitney U test, as appropriate. All analyses were performed by means of STATA 17 statistical software, and statistical significance was set at $p<0.05$.

RESULTS

Table 1 shows demographic, clinical characteristics and outcomes of the 90 patients enrolled in this study. During the outbreak period, a total of 178 inpatients (140 from UH and 38 from PH) acquired SARS-CoV-2 infection, and 47 of them received remdesivir within a median time of 1.4 days from testing positive.
The 43 patients who were enrolled as controls did not receive remdesivir due to various reasons, such as refusal, or medical judgment of not being particularly at high risk of progression, or the fact that more than 5 days had passed from infection onset. A total of 28 UH patients did not receive remdesivir: 18 cases for medical judgment of not being particularly at high risk of progression, 3 cases for eGFR <30 ml/min, 5 cases for terminal status, 1 case for refusal, and 1 patient who was treated with molnupiravir. A

Table 1 - *Demographic, clinical characteristics and outcomes.*

	Cases (N= 47)	*Controls (N= 43)*	*p-value*
Age (years), mean ± standard deviation	74.5 ±10.2	73.5 ±15.6	0.862
Male gender, N (%)	25 (53.2)	27 (62.8)	0.357
Previous symptomatic SARS-CoV-2 infection, N (%)	1 (2.1)	2 (4.7 %)	0.604
Vaccination, N (%)			0.896
None	8 (17.0)	8/41 (19.5)	
1-2 doses	17 (36.2)	13/41 (31.7)	
3 doses[1]	22 (46.8)	20/41 (48.8)	
Reasons for hospitalization, N (%)			0.078
Congestive heart failure	2 (4.3)	9 (20.9)	
Sepsis	5 (10.6)	5 (11.6)	
Acute kidney injury	0 (0)	1 (2.3)	
Respiratory failure	8 (17)	3 (7)	
Neoplasia	13 (27.7)	10 (23.3)	
Stroke	3 (6.4)	0 (0)	
Other	16 (34)	15 (34.9)	
Time from positive testing after contact (days), median (IQR)	2 (1-3)	2 (1-3.5)	0.869
Time of first remdesivir infusion from testing positive			–
Mean time (days)	1.6	NA	
Median time (days)	1.4	NA	
Adverse events to remdesivir, N (%)	0 (0)	NA	–
Progression to severe pneumonia requiring supplemental oxygen or non-invasive ventilation, N (%)	4 (8.5)	7 (16.3)	0.261
In-hospital overall mortality, N (%)	8 (17)	7 (16.3)	0.925
Discharge delay due to SARS-CoV-2 infection (days), median (IQR)	3 (0-11)	0 (0-2)	0.008

[1]Patients vaccinated with one dose of Vaxzevria® and Jcovden® vaccines plus one booster of Comirnaty® and Spikevax® were considered as fully vaccinated as three doses of Comirnaty® or Spikevax®.

total of 15 PH patients did not receive remdesivir: 10 cases for eGFR <30 ml/min, 1 case for body weight <40 kg, 1 case for terminal status, 1 case for refusal; 2 patients who were treated with sotrovimab.

No significant differences were observed between cases and controls on mean age, sex, vaccination status, previous symptomatic SARS-CoV-2 infection, reasons for hospitalization.

There were no adverse events in the remdesivir-treated group.

No patient treated with remdesivir died due to COVID-19: all 8 deaths observed among cases were due to the progression of a pre-existing oncological disease, a frequent cause of hospitalization both among cases and controls (25.6%). Notably, no significant differences in overall in-hospital mortality were observed in cases compared to controls (17% *vs* 16.3%, p=0.925).

Progression to severe pneumonia requiring supplemental oxygen or non-invasive ventilation showed an evident trend toward favorable outcomes for cases compared to controls (8.5% *vs* 16.3%, p=0.261), but this difference was not significant.

Finally, a significantly increased median discharge delay of 3 days (p=0.008) was assessed for the group of patients treated with remdesivir.

Most of the patients who acquired SARS-CoV-2 infection remained asymptomatic or pauci-symptomatic.

DISCUSSION

In this study the progression to severe pneumonia requiring supplemental oxygen or non-invasive ventilation was lower, almost halved, for cases compared to controls: this difference was not significant, but this may possibly be explained by the limited sample size which did not allow for statistical significance in the observed difference. Notably, the percentage of severe pneumonia reported among our untreated patients (16.3%) is quite similar to the 15-20% reported in the literature (Huang *et al*., 2020); therefore, the percentage of 8.5% observed in patients treated early with remdesivir seems very interesting.

In the group treated with remdesivir, the acquisition of SARS-CoV-2 infection during an otherwise "standard" hospitalization led to a significantly increased median discharge delay of 3 days compared with untreated patients (p=0.008), with significant economic implications for the healthcare system. Surely, this delay in discharge would be acceptable only if benefit from treatment could be demonstrated: unfortunately, as noted above, and possibly due to the small sample size, we could only highlight a clear, but not statistically significant, trend concerning progression toward severe forms of disease.

Unlike studies on early use of antivirals (Gottlieb *et al*., 2022, Hammond *et al*., 2022, Jayk Bernal *et al*.,

2022), most of our patients were vaccinated: only 17% of cases and 19.5% of controls were unvaccinated. We could not estimate how vaccination may have affected the outcomes observed: the sample size seems too small to perform subgroup analyses to detect any difference in the clinical course of patients who completed the primary vaccination course and those who did not. We cannot assess if remdesivir is more effective in vaccinated or unvaccinated inpatients.

In addition, disease severity and the relative effectiveness of remdesivir treatment could be impacted by the less severe Omicron variant (Nyberg *et al*., 2022) circulating in the study period.

The main limitation of our study, based on real-world data, is represented by its retrospective design. Our data are descriptive, and relate only to a small population of patients. Readers should put the findings of this study in context to avoid wrong conclusions. In fact, randomized-controlled studies designed with adequate methodology in this setting should be carried out to specifically assess this topic.

In conclusion, an early 3-day course of remdesivir seems have an excellent safety profile and might prevent disease progression among high-risk patients acquiring SARS-CoV-2 infection during hospitalization.

Declaration of interest statement

All authors have no conflicts of interest to declare.

References

Angamo M.T., Mohammed M.A., Peterson G.M. (2022). Efficacy and safety of remdesivir in hospitalised COVID-19 patients: a systematic review and meta-analysis. *Infection*. **50** (1): 27-41.

Beigel J.H., Tomashek K.M., Dodd L.E., Mehta A.K., Zingman B.S., Kalil A.C, et al.; ACTT-1 Study Group Members. (2020). Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med*. **383** (19): 1813-1826.

Dölken L., Stich A., Spinner C.D. (2021). Remdesivir for Early COVID-19 Treatment of High-Risk Individuals Prior to or at Early Disease Onset-Lessons Learned. *Viruses*. **13** (6): 963.

Goldman J.D., Lye D.C.B., Hui D.S., Marks K.M, Bruno R., Montejano R., et al. GS-US-540-5773 Investigators. (2020). Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med*. **383** (19): 1827-1837.

Gottlieb R.L., Vaca C.E., Paredes R., Mera J., Webb B.J., Perez G., et al.; GS-US-540-9012 (PINETREE) Investigators. (2022). Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *N Engl J Med*. **386** (4): 305-315.

Hammond J., Leister-Tebbe H., Gardner A., Abreu P., Bao W., Wisemandle W., et al.; EPIC-HR Investigators. (2022). Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. *N Engl J Med*. **386** (15): 1397-1408

Huang H., Cai S., Li Y., Li Y., Fan Y., Li L., et al. (2020). Prognostic Factors for COVID-19 Pneumonia Progression to Severe Symptoms Based on Earlier Clinical Features: A Retrospective Analysis. *Front Med* (Lausanne). **7**: 557453.

Jayk Bernal A., Gomes da Silva M.M., Musungaie D.B., Kovalchuk E., Gonzalez A., Delos Reyes V., et al.; MOVe-OUT Study Group. (2022). Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. *N Engl J Med*. **386** (6): 509-520.

Nyberg T., Ferguson N.M., Nash S.G., Webster H.H., Flaxman S., Andrews N., et al. (2022). Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet*. **399** (10332): 1303-1312.

Wölfel R., Corman V.M., Guggemos W., Seilmaier M., Zange S., Müller M.A., et al. (2020). Virological assessment of hospitalized patients with COVID-2019. *Nature*. **581** (7809): 465-469.