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Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: Clinical outcome and differences in post-treatment hospitalisation status

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ABSTRACT

SARS-CoV-2 is causing an increasing number of deaths worldwide because no effective treatment is currently available. Remdesivir has shown *in vitro* activity against coronaviruses and is a possible antiviral treatment for SARS-CoV-2 infection.

This prospective (compassionate), open-label study of remdesivir, which was conducted at Luigi Sacco Hospital, Milan, Italy, between February 23 and March 20, 2020, involved patients with SARS-CoV-2 pneumonia aged ≥18 years undergoing mechanical ventilation or with an oxygen saturation level of ≤94 % in air or a National Early Warning Score 2 of ≥4. The primary outcome was the change in clinical status based on a 7-category ordinal scale (1 = not hospitalised, resuming normal daily activities; 7 = deceased).

The 35 patients enrolled from February 23 to March 20, 2020, included 18 in intensive care unit (ICU), and 17 in our infectious diseases ward (IDW). The 10-day course of remdesivir was completed by 22 patients (63 %) and discontinued by 13, of whom eight (22.8 %) discontinued because of adverse events. The median follow-up was 39 days (IQR 25–44). At day 28, 14 (82.3 %) patients from IDW were discharged, two were still hospitalized and one died (5.9 %), whereas in ICU 6 (33.3 %) were discharged, 8 (44.4 %) patients died, three (16.7 %) were still mechanically ventilated and one (5.6 %) was improved but still hospitalized. Hypertransaminasemia and acute kidney injury were the most frequent severe adverse events observed (42.8 % and 22.8 % of the cases, respectively).

Our data suggest that remdesivir can benefit patients with SARS-CoV-2 pneumonia hospitalised outside ICU where clinical outcome was better and adverse events are less frequently observed. Ongoing randomised controlled trials will clarify its real efficacy and safety, who to treat, and when.

1. Introduction

Since the first reported outbreak in Wuhan, China, in December 2019, the world has witnessed the pandemic spread of the newly identified *Betacoronavirus* SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) that is responsible for coronavirus disease-19 (COVID-19) [1–3]. After a few sporadic cases in nine European countries, Italy became one of the western countries with the highest

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number of diagnosed cases (203,591 as of 29 April 2020), with the greatest outbreak occurring in the region of Lombardy (75.134 cases) [4,5].

SARS-CoV-2 spreads from human to human transmission by means of respiratory droplets or direct contact, and has a median incubation period of 5.1 days and a basic reproduction number of 2.24–3.58 [6,7]. The clinical spectrum of COVID-19 ranges from mild disease (i.e. the absence of pneumonia or mild pneumonia) in about 80 % of cases to life-threatening pneumonia in the form of acute respiratory disease syndrome (ARDS) requiring intensive care in 6% [8–11]. The case fatality rate (CFR) seems to vary and reported estimates range from 1% to 7%, but this should be more precisely known once surveillance studies have clarified the number of infected subjects [12,13].

Given the severity and expected high CFR of the pneumonia caused by SARS-CoV-2, it is imperative to find an effective drug treatment because supportive care and oxygen supplementation is not always enough. Remdesivir, a nucleoside pro-drug that is thought to act by inhibiting viral RNA transcription, has shown *in vitro* antiviral activity against bat coronavirus and SARS-CoV-2, and has been safely used in one patient with SARS-CoV-2 pneumonia in the USA [14–17].

This study evolved in the context of the emergency caused by the large outbreak of COVID-19 in Lombardy, Italy, that started on 20 February 2020. On 21 February, the pharmaceutical company Gilead Sciences agreed to a request for the donation of remdesivir for compassionate use in individual patients seriously affected by SARS-CoV-2 pneumonia and hospitalised at Luigi Sacco Hospital, Milan, Italy. A report containing the clinical information and laboratory test results of each eligible patient requiring oxygen supplementation was sent to Gilead for approval. Enrolment in the programme ended on March 20, 2020 as it was planned to start a randomised, controlled, double-blind clinical trial aimed at evaluating the efficacy and safety of remdesivir in hospitalised patients with mild to moderate COVID-19 respiratory disease [18]. Pending the results of this trial, we report the outcomes of 35 patients who received compassionate remdesivir treatment during the first days of the Italian SARS-CoV-2 epidemic.

2. Patients and methods

2.1. Patients and treatment schedule

Patients were eligible to receive remdesivir for compassionate use if they were a male or non-pregnant female aged $\geq$18 years, had SARS-CoV-2 infection confirmed by a positive reverse-transcriptase polymerase chain reaction (RT-PCR) test of a respiratory tract sample and pneumonia confirmed by a chest X-ray or computed tomography (CT) scan, and were mechanically ventilated or had an oxygen saturation (SaO2) level of $\leq$94 % in room air or a National Early Warning Score (NEWS)2 of $\geq$ 4 [19]. Patients were excluded if their alanine or aspartate aminotransferase level was > 5 times the upper limit of the normal range and creatinine clearance was < 30 mL/min.

Urgent approval for each eligible patient was obtained by our Ethics Committee and sent to Gilead together with the patient's clinical history. Written informed consent was obtained from all of the patients except those who were undergoing invasive mechanical ventilation, for whom the principle of urgency was applied.

The patients were prospectively enrolled in the remdesivir treatment programme between 23 February and March 20, 2020 (Fig. 1). The drug schedule was an intravenous loading dose of 200 mg on day 1, followed by an intravenous dose of 100 mg/day from day 2 to day 10. The patients could continue their existing treatments including hydroxychloroquine (HCQ), but had to discontinue lopinavir/ritonavir (LPV/r) in accordance with Gilead's recommendations.

The clinical and laboratory data of all of the patients who received at least one dose of remdesivir were collected on a daily basis from the date of enrolment to the date of discharge, death or censoring (20 April 2020) (Fig. 2).

In a subset of patients, a semi-quantitative RT-PCR test of a nasopharyngeal swab was carried out at baseline and during remdesivir treatment using an automated ELITe InGenius® system and the GeneFinder™ COVID-19 Plus RealAmp Kit (ELITechGroup, France). The reaction mix was manually prepared in accordance with the manufacturer's instructions, and loaded on to the system with other reagents, and RNA was extracted from 200 µL of sample and eluted in 100 µL; the final reaction volume consisted of 5 µL of RNA plus 15 µL of reagent mix. The RT-PCR profile was 50 °C for 20 min, 95 °C for five minutes plus 45 cycles at 95 °C for 15 s and 58 °C for 60 s in accordance with the manufacturer's instructions. Three target genes, RNA-dependent RNA polymerase (RdRP), nucleocapsid protein (N) and envelope membrane protein (E) were simultaneously amplified and tested. Viral load was measured as the cycle threshold (Ct) value.

2.2. Outcome measures

The primary outcome was the change in the patients' hospitalisation status on the 10th and 28th day of treatment. Hospitalisation status was assessed using a 7-category ordinal scale previously used in influenza studies [20], in which 1 = not hospitalised, capable of resuming normal activities; 2 = not hospitalised but unable to resume normal activities; 3 = hospitalised, not requiring oxygen supplementation; 4 = hospitalised and requiring oxygen therapy; 5 = hospitalised an requiring high-flow nasal oxygen therapy, non-invasive mechanical ventilation, or both; 6 = intensive care unit (ICU) hospitalisation, requiring invasive mechanical ventilation or extra corporeal membrane oxygenation (ECMO), or both; 7 = deceased.

The secondary outcome was safety, including adverse events leading to premature treatment discontinuation. Adverse events were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

2.3. Statistical analysis

Continuous variables are expressed as median values and their interquartile range (IQR), and were compared using the non-parametric Mann-Whitney test; categorical variables are expressed as absolute numbers and percentages, and were compared using Fisher's exact test. Friedman's test was used for paired samples.

3. Results

Between 23 February and 20 March 2020, 50 consecutive patients (fully representative of all hospitalised COVID-19 patients in Italy) were evaluated for the compassionate use of remdesivir and 48 were considered eligible for treatment. Thirteen patients did not start the drug for the reasons given in Fig. 1. The remaining 35 received at least one dose and were evaluated for the outcomes of interest. Thirty-one of these patients had previously received LPV/r + HCQ for a median of five days, but all discontinued LPV/r upon enrolment.

Eighteen patients started remdesivir in our ICU and seventeen in our Infectious Disease ward (IDW): most of ICU patients were undergoing invasive mechanical ventilation, and most of the IDW patients were undergoing high-flow oxygen therapy and/or non-invasive mechanical ventilation.

Table 1 shows the main baseline characteristics of the ICU and IDW patients, who were prevalently males (77.8 % and 70.6 %) and had a median age of respectively 60.5 (IQR 49.25–63.75) and 64.0 years (IQR 51.0–75.0). The median time from symptom onset to hospital admission was seven days in both groups, whereas the median time from hospital admission to the start of remdesivir treatment was shorter in the ICU than in the IDW patients (4 days, IQR 3.0–5.0 *vs* 5 days, IQR 4–6). The median Charlson Comorbidity Index was 2 in the ICU group and 2 in the IDW group, and most frequent co-morbidity in both groups was hypertension (27.8 % and 41.2 %). The median NEWS2 score was higher

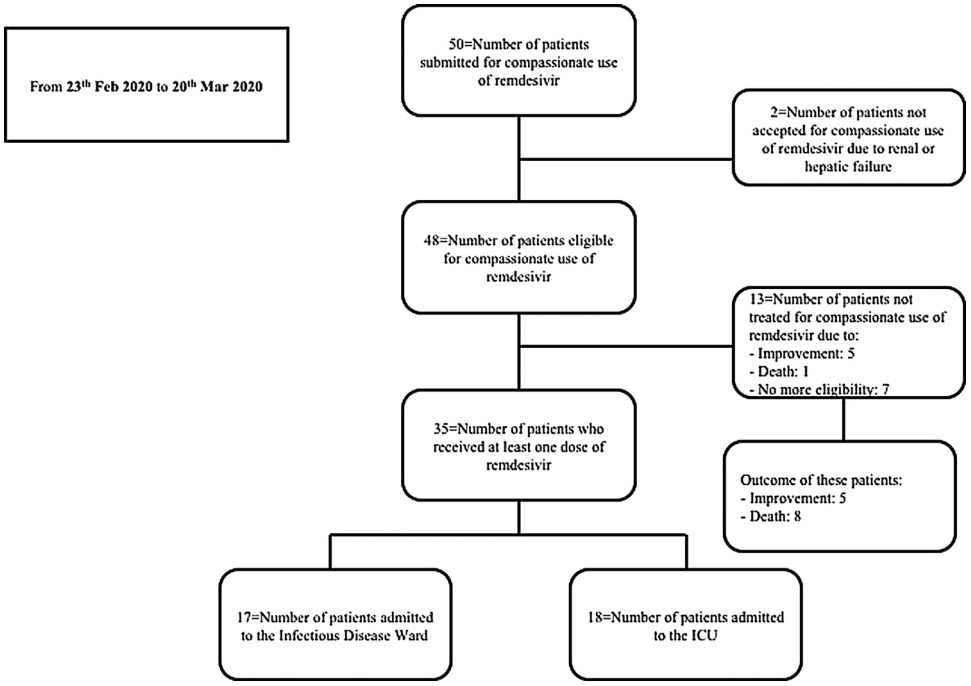

Fig. 1. Study flow chart.

in the ICU than in the IDW patients (6 *vs* 4), and they also had a higher median white blood cell count (7640/μL *vs* 6580/μL) and D-dimer level (5632.5 *vs* 1306), a lower absolute lymphocyte count (625/μL *vs* 890/μL), and higher C-reactive protein (177 *vs* 106) and LDH levels (559 U/L *vs* 399 U/L).

Twenty-two (63 %) completed the scheduled course of remdesivir, whereas thirteen (nine in ICU and four IDW patients) had the treatment discontinued after a median of five doses (IQR 4–6) because of toxicities (n = 8, 22.8 %), death (n = 4, 11.4 %) and early discharge (n = 1, 2.9 %).

3.1. Primary outcomes

As shown in Fig. 2, by day 10 of rendesivir treatment, four (22.2 %) of the ICU patients showed an improvement in their hospitalisation status (one was still hospitalised but not requiring supplemental oxygen and three had been weaned from invasive ventilation), ten (55.5 %) were still undergoing invasive ventilation, and four (22.2 %) had died; by the 28 day of follow-up, the hospitalisation status of 38.9 % of the ICU patients had improved (six had been discharged, one had been weaned from invasive ventilation), 16.7 % were still undergoing mechanical ventilation and the other 44.4 % had died.

Among the IDW patients, the hospitalisation status of 6 (35.3 %)

Table 1
Baseline demographic and clinical characteristics of the patients.

Characteristic	Total (n = 35)	ICU patients (n = 18)	IDW patients (n = 17)
Age (years), median (IQR)	63.0 (51.0 – 69.0)	60.5 (49.2 – 63.7)	64.0 (51.0 – 75.0)
Males, n (%)	26 (74.3)	14 (77.8)	12 (70.6)
Time from onset of symptoms to hospitalisation (days), median (IQR)	7.0 (5.0 – 10.0)	7.0 (6.0 – 10.0)	7.0 (5.0 – 9.0)
Median time from hospitalisation to start of remdesivir (days), median (IQR)	4.0 (3.0 – 5.0)	4.0 (3.0 – 5.0)	5.0 (4.0 – 6.0)
Charlson Comorbidity Index, median (IQR)	2.0 (1.0 – 3.0)	2.0 (1.0 – 2.0)	2.0 (1.0 – 3.0)
Co-existing conditions, n (%)			
- Diabetes	3 (8.6)	3 (16.7)	–
- Hypertension	12 (34.3)	5 (27.8)	7 (41.2)
- Cancer	1 (2.9)	1 (5.6)	–
- Obesity	3 (8.6)	2 (11.1)	1 (5.9)
FiO_2, median (IQR)	0.6 (0.50 – 0.80)	0.7 (0.52 – 0.80)	0.6 (0.40 – 0.60)
PaO_2/FiO_2 ratio, median (IQR)	129.5 (110.2 – 161.0)	133.0 (115 – 171)	124 (106.7 – 139.5)
NEWS2, median (IQR)	5.5 (4.0 – 6.7)	6.0 (5.0 – 87)	4.0 (3.0 – 6.0)
Body temperature (°C), median (IQR)	37.0 (36.0 – 37.9)	37.0 (36.0 – 37.6)	37.0 (36.0 – 38.5)
WBC (10^9/L), median (IQR)	7.2 (5.9 – 9.1)	7.6 (6.5 – 9.5)	6.6 (5.8 – 7.7)
Lymphocytes (10^9/L), median (IQR)	0.67 (0.5 – 1.2)	0.62 (0.45 – 0.98)	0.89 (0.57 – 1.18)
Platelets (10^9/L), median (IQR)	249 (194.0 – 316.0)	252 (216.0 – 303.0)	249(191.0 – 313.0)
Prothrombin (INR), median (IQR)	1.40 (1.19 – 1.54)	1.40 (1.21 – 1.55)	1.38 (1.19 – 1.53)
D-dimer (μg/L), median (IQR)	4011 (1406 – 14400)	5632 (2509 – 12977)	1306 (646 – 13992)
Alanine aminotransferase (U/L), median (IQR)	43 (20.0 – 57.5)	48.5 (18.7 – 62.7)	34.0 (20 – 50)
Lactate dehydrogenase (U/L), median (IQR)	492 (364 – 587)	559 (445 – 672)	399 (352 – 475)
C-reactive protein (mg/L), median (IQR)	106.0 (54.5 – 262)	177.0 (57 – 311)	106 (55 – 185)
Serum creatinine (mg/dL), median (IQR)	1.01 (0.68 – 1.24)	0.95 (0.64 – 1.48)	1.01 (0.82 – 1.16)

ICU, intesive care unit; IDW, infectious diseases ward; IQR, interquartile; FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen, NEWS2, National Early Warning Score 2; WBC, white blood cells.

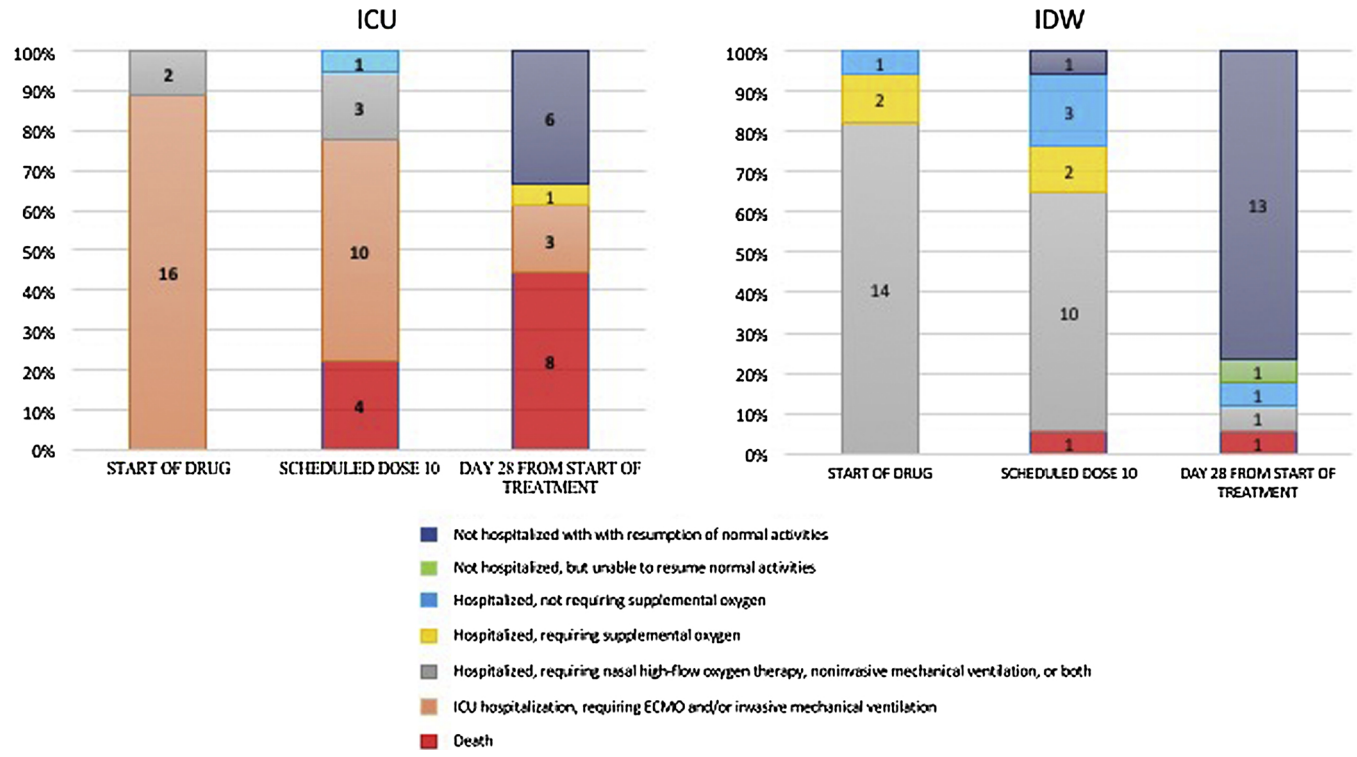

Fig. 2. Clinical outcomes based on the 7-category ordinal scale endpoints.

had improved by day 10 of remdesivir treatment (one had been discharged, three no longer required oxygen supplementation, and, two were still hospitalised but no longer required high-flow therapy and/or non-invasive mechanical ventilation); but 10 still required high-flow therapy and/or non-invasive mechanical ventilation, and one had died. By day 28 of follow-up, hospitalisation status had improved in 88.2 % of the IDW patients (14 had been discharged, one no longer required oxygen supplementation) but one still required high-flow therapy and/or non-invasive mechanical ventilation.

3.2. Other clinical examinations and laboratory tests

The NEWS2 and laboratory test results of fourteen ICU and 15 IDW patients could be assessed on day 10 of remdesivir treatment. There were no statistically significant changes from baseline in NEWS2 in either group, but the IDW patients (although not the ICU patients) showed a statistically significant improvement in FiO_2 values ($p = 0.046$). Moreover, there was a statistically significant increase in lymphocyte counts in both the ICU and IDW groups ($P = < 0.001$ and $P = 0.001$), and a statistically significant decrease in C-reactive protein levels ($P = 0.002$ and $P < 0.001$).

Twenty-one of the 35 enrolled patients (seven ICU and fourteen IDW patients) were tested for SARS-CoV-2 viral load on a nasopharyngeal swab at baseline and during treatment. The overall median value at baseline was 25 Ct (27 in the ICU and 25 in the IDW patients), and 22 had a negative viral load a median of 12 days (IQR 9.25–16.75) after the start of remdesivir treatment.

3.3. Safety

Table 2 shows severe adverse events recorded during remdesivir treatment. The most frequent was hepatotoxicity, with a grade 3–4 increase in transaminases levels observed in 42.8 % of the patients. The most frequent adverse event leading to treatment discontinuation was acute kidney injury (AKI), which was observed in four patients, all in ICU, three of whom eventually died. Remdesevir was also discontinued in three patients showing a grade 3–4 increase in transaminase levels, and in one patients who developed a serious maculo-papular rash.

Table 2
Severe adverse events (AEs) in patients with SARS-CoV-2 pneumonia receiving remdesivir.

Event	Total n = 35	ICU n = 18	IDWn = 17
Reported grade 2 – 3 AEs			
Hypertransaminasemia	15 (42.8 %)	8 (44.4 %)	7 (41.2 %)
Increased total bilirubin levels	7 (20.0 %)	2 (11.1 %)	5 (29.4 %)
Acute kidney injury	8 (22.8 %)	7 (38.8 %)	1 (5.9 %)
Rash	2 (5.7 %)	–	2 (11.8 %)
Any AE leading to treatment discontinuation	8 (22.8 %)	6 (33.3 %)	2 (11.7 %)

4. Discussion

The pandemic emergence of SARS-CoV-2 infection, which is characterised by progressively severe pneumonia and ARDS that leads to a high mortality rate among hospitalised patients, challenges the medical community to evaluate rapidly any possibly effective antiviral drug [21]. On the basis of *in vitro* studies of different coronaviruses (including SARS-CoV-2), it seems that a number of drugs may be candidate treatment options, including LPV/r, chloroquine, HCQ and remdesivir [14–16,22–25]. One randomised, controlled trial of LPV/r involving hospitalised patients with severe COVID-19 has failed to demonstrate any clinical benefit [26].

Remdesivir, a broad-spectrum antiviral drug used in the treatment of Ebola virus, has shown *in vitro* activity against SARS-Cov-2 [16], and various phase II and III randomised clinical trials of parenteral remdesivir involving patients with mild-to-moderate and severe COVID-19 are currently ongoing in Europe and the USA [18]. So far, two single case reports and a multinational compassionate treatment study have suggested a beneficial effect of remdesivir for patients with severe

COVID-19 pneumonia [17,27,28]. Conversely, in a randomised, double-blind placebo-controlled study conducted in China, remdesivir was not associated with statistically significant beneficial clinical outcome with severe COVID-19 pneumonia [29]. This later study, however, has been stopped earlier due to the reduction of the number of COVID-19 cases in China and it was therefore underpowered to provide conclusive information.

We report, our experience of remdesivir compassionate use in 35 patients treated at Luigi Sacco Hospital in Milan, Italy, between 23 February and 20 March 2020, of whom 63 % completed the 10-day course, and 37 % discontinued it prematurely because of adverse events. The hospitalisation status of 88.2 % of our IDW patients improved by the day 28 from starting remdesivir treatment, the majority of whom had been discharged to resume their normal activities; however, there was a 44.4 % case fatality rate among the patients who started the treatment in our ICU. Given that the clinical condition of only one of our IDW patients worsened, it is possible that remdesivir may be more efficacious in patients who present early in a non-critical condition. As has been shown in a previous study of the use of neuraminidase inhibitors against influenza [30], a delay in beginning antiviral treatment can be crucial when evaluating the efficacy of drugs against an acute respiratory infection.

Interestingly, we were able to measure SARS-CoV-2 viral load in nasopharyngeal swabs of 21 of our patients at baseline and during remdesivir treatment, and the RT-PCR showed that all of these patients became negative a median of 12 days after the start of treatment. This is in line with with the rapid decline in viral load observed in a single patient treated with remdesivir in the USA [17], and these may cautiously considered a positive virological response, given that a study conducted in Wuhan showed that the median duration of viral shedding among patients surviving SARS-CoV-2 infection was 20 days [9].

One-third of the patients enrolled in our study were unable to complete the scheduled 10-day course of remdesivir because of AEs. The most frequent severe AE was increase in liver enzymes, a finding in line with data of the multicenter compassionate study by Grein et al. [28]. Moreover, four of our patients who started remdesivir treatment in the ICU developed AKI, and three of them eventually died; however, it is difficult to say whether the AKI was caused by the infection itself, remdesivir, or any of the other administered medications. Since LPV/r was discontinued 24 h before the administration of remdesivir we believe that the AEs were likely independent of that previous treatment although it cannot fully excluded.

We acknowledge that our study has a number of limitations. First, given the context in which it originated, it was impossible to include a control group so we cannot exclude the possibility that the patients whose hospitalisation status improved after remdesivir treatment may have improved regardless of any treatment. Secondly, most of our patients had previously received LPV/r + HQC and this may represent a confounding factor when analysing the efficacy of remdesivir. Finally, we could not predefine a virological follow-up which limits our finding of a possible virological effect of remdesivir in inducing the clearance of viral RNA in the patients' respiratory samples.

In conclusion, remdesivir treatment may have a beneficial effect on SARS CoV-2 pneumonia, especially in the case of non-critically ill patients. Our decision to administer it for compassionate use was triggered by a state of emergency, but randomised controlled trials are now needed to determine the safety and efficacy of remdesivir and any other investigational agent in the treatment of patients with SARS CoV-2 infection.

Declaration of competing interest

SA received support for research activities from Pfizer, MSD, and Boehringer Ingelheim; SR received grants, fees for speaker's- bureau, advisory boards and CME activities from BMS, ViiV, MSD, AbbVie, Gilead, Janssen; AG received consultancy fees from Mylan and non-financial support from Gilead. GR received grants, fees for speaker's bureau, advisory boards and CME activities from BMS, ViiV, MSD, AbbVie, Gilead, Janssen and Roche; MG received grants, fees for speaker's bureau, advisory boards and CME activities from BMS, ViiV, MSD, AbbVie, Gilead, Janssen and Roche; MVC, ALR, RR, CB, GP, GG, MC, CM, AC, BB, RC, RG, EA, DM, LM, SV, MC, AT, LO, MRG, LM have nothing to declare.

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