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.

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Letter to the Editor

Remdesivir in moderate to severe COVID-19: A matter of time?

Dear Editor,

Since the first days of SARS-CoV-2 pandemic, many repurposed drugs have been used in a compassionate way ranging from antivirals (*i.e.* lopinavir/ritonavir and remdesivir) and immune-modulators (*i.e.* hydroxychloroquine) in hospitalised COVID-19 patients [1]. As previously described in the Journal by our group, during the early days of the pandemic the inhibitor of the viral RNA-dependent RNA polymerase named remdesivir was administered in compassionate way irrespectively from the disease severity without a clear clinical benefit especially in critically ill COVID-19 patients [2]. A subsequent randomised clinical trial led to the authorisation of remdesivir for COVID-19 treatment [3], although a marginal benefit in shortening the time to recovery was observed only in patients with moderate disease without a clear impact on COVID-19 related mortality [4]. Thus, many countries, such as Italy, approved upon conditional marketing authorisation this drug in all hospitalised COVID-19 patients requiring oxygen supply in June 2020. In Italy, the Italian Medicines Agency (AIFA) restricted in November the prescription of remdesivir only to patients with radiologically documented pneumonia without the requirement of high-flow oxygen and symptoms' onset of less than 10 days [5]. The rational of an early start of remdesivir rely on its theoretical antiviral efficacy which should be as high the earlier the infection is as demonstrated in non-human primate models [6]. Nevertheless, the clinical relevance of the effect of time to remdesivir administration and COVID-19 related outcomes is still matter of debate.

With this in mind, we aimed to retrospectively assess the use of remdesivir in the Luigi Sacco COVID-19 registry after the marketing registration in June 2020 looking at the association between time to remdesivir exposure after oxygen support requirement and COVID-19 related outcomes.

The characteristics of the centre such as data collection of Luigi Sacco COVID-19 registry have been described elsewhere [7]. For the purpose of the present analysis were included all subjects with a moderate to severe COVID-19 [7] treated with at least one dose of remdesivir from the market approval of the drug in June 2020 to 31st December 2020. Patients with a symptoms' onset of more than 10 days and requiring high flow oxygen support, invasive or non-invasive ventilation before the remdesivir start were excluded. All patients were also treated with the standard of care at our centre: best oxygen support, dexamethasone 6 mg for 10 days and prophylactic antithrombotic therapy. The primary outcome of interest was composite: non-invasive ventilation or invasive ventilation or death whichever occurred first. Kaplan Meier curves were built to estimate the overtime probability of primary outcome occurrence by stratifying the group according to remdesivir start in days from oxygen support requirement (≤ 1 *vs* > 1). The association between time from oxygen support requirement to remdesivir start and the primary outcome was assessed by means of univariable and multivariable Cox proportional hazard models. All of the statistical analyses were made using SAS software, version 9.4, and a p value of < 0.05 was considered statistically significant. The study was approved by our Comitato Etico Interaziendale Area 1.

During the study period 131 patients were treated with remdesivir in addition to the standard of care of whom 87 (66%) met the inclusion criteria for the present analysis. Baseline characteristics of the study population are reported in Table 1. Twenty-seven patients (31%) received remdesivir within 1 day from oxygen support start whereas the remaining 60 (69%) thereafter. There were no significant between-group differences in terms of number and type of comorbidities, time from symptoms onset to oxygen requirement and disease severity.

Patients treated within one day from oxygen support start less frequently required non-invasive ventilation when compared to those who started the drug after one day (11% *vs* 45%; $p = 0.003$) whereas no significant differences were observed in terms of invasive ventilation requirement (7.4% *vs* 10%; p = 0.999) or death (11.1% *vs* 18.3%; p = 0.535).

The protocol defined outcome occurred less frequently in subjects exposed to remdesivir within one day from oxygen support start when compared to those who started the drug after one day [Hazard Ratio (HR): 0.33 (95% Confidence Interval (CI)) 0.00–0.86; $p = 0.023$]. After adjusting into the multivariable Cox model for age, biological sex, time from symptoms onset and obesity the start of remdesivir within one day from oxygen support start confirmed to be associated to a reduced probability of occurrence of the protocol defined outcome [adjusted HR: 0.36 (95% CI 0.00–0.96); $p = 0.041$].

In our study an association between early remdesivir administration, within one day from oxygen support, in combination with the standard of care and a reduced probability of disease progression was observed.

Considering the natural history of SARS-CoV-2 infection, the potential progression to pneumonia with the requirement of oxygen supply usually occurs some days after the symptoms' onset. Thus, it is likely that most of the potential beneficial effect of a theoretical antiviral treatment, such as remdesivir, could fade away as far as the time from the infection increases. Considering the clinical scenario of our centre where most of patient presents for hospital care after a median of 6 days from symptoms onset, the question is if a fast remdesivir administration could improve the intrahospital outcomes in terms of reducing requirement of invasive or non-invasive ventilation and/or death in COVID-19 patients with moderate to severe disease. According to our results an association between a shorter time ($\leq$ 1 day) from oxygen support requirement to remdesivir administration and better composite outcome has been observed in patient ranging from moderate to severe COVID-19. Our findings are in line with registration trial which support the use of the drug in subject with moderate disease [3]. In the same trial in the subgroup analysis from time to symptoms onset a significant

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Table 1
Characteristics of patients treated with remdesivir according to being exposed to remdesivir within one day from oxygen requirement or thereafter.

	Overall n = 87	Time from O2 to remdesivir start ≤ 1 day n = 27	Time from O2 to remdesivir start > 1 day n = 60	*p*
Age, median (IQR)	67.7 [56.1–77.7]	67.7 [55.2–81.7]	67.4 [56.6–75]	0.650
Biological sex, n (%)				
Female	19 (21.8)	9 (33.3)	10 (16.7)	0.098
Male	68 (78.2)	18 (66.7)	50 (83.3)	
Comorbidities, n (%)				
Obesity	21 (24.1)	7 (25.9)	14 (23.3)	0.792
Diabetes	16 (18.4)	4 (14.8)	12 (20.0)	0.766
Lung diseases	19 (21.8)	7 (25.9)	12 (20.0)	0.581
Heart diseases	49 (56.3)	12 (44.4)	37 (61.7)	0.164
Metabolic disorders	32 (36.8)	9 (33.3)	23 (38.3)	0.811
Renal diseases	6 (6.9)	1 (3.7)	5 (8.3)	0.661
Oncological diseases	14 (16.1)	3 (11.1)	11 (18.3)	0.535
Immune system disorders	6 (6.9)	1 (3.7)	5 (8.3)	0.661
Liver diseases	5 (5.7)	1 (3.7)	4 (6.7)	0.999
Number of comorbidities, n (%)	23 (26.4)	10 (37.0)	13 (21.7)	0.476
0	21 (24.1)	5 (18.5)	16 (26.7)	
1	26 (29.9)	8 (29.6)	18 (30.0)	
2	17 (19.5)	4 (14.8)	13 (21.7)	
3+				
Time from symptoms onset, median (IQR)	6.0 [4.0, 8.0]	7.0 [5.5–8.0]	6.0 [4.0–7.0]	0.160
Disease severity (%)				0.161
Moderate	35 (40.2)	14 (51.9)	21 (35.0)	
Severe	52 (59.8)	13 (48.1)	39 (65.0)	

List of abbreviations: n, number; IQR, Inter Quartile Range.

advantage was only observed in patients with a symptoms onset ≤ 10 days (Recovery rate 1.37 (95% CI 1.14–1.64)) [3]. Nevertheless, no effect on mortality or invasive ventilation requirement was observed suggesting that the effect of remdesivir would only be marginal when considering these two major outcomes as observed in previous randomised clinical trials [3,4].

Our findings should also be interpreted with caution in light of the intrinsic limitation of the study design. First, the choice to administer remdesivir was based on single clinical judgement. Second, it is impossible to distinguish between the effect of remdesivir and the underlying standard of care composed by dexamethasone and prophylactic antithrombotic drugs. Third, the sample size is small and it cannot be excluded that our observation could be chance driven. In the end, unmeasured residual confounders could explain the observed association between a shorter time to remdesivir administration and the investigated outcome.

In conclusion, we observed better clinical outcomes in COVID-19 patients with moderate to severe disease who started remdesivir in association with the standard of care within one day from oxygen support start. Considering the limited additive benefit of remdesivir in term of major clinical outcomes, our findings underline the need of an early initiation of this drug to maximise its potential clinical benefits.

Conflict of interest

Dr. Giacomelli received funding from consultancy fees from Mylan and educational support from Gilead. Dr. Antinori has received support for research activities from Pfizer and Merck Sharp & Dome. The remaining authors have disclosed that they do not have any potential conflicts of interest.

References

[1] A. Giacomelli, G. Pagani, A.L. Ridolfo, L. Oreni, F. Conti, L. Pezzati, L. Bradanini, G. Casalini, C. Bassoli, V. Morena, S. Passerini, G. Rizzardini, C. Cogliati, E. Ceriani, R. Colombo, S. Rusconi, C. Gervasoni, D. Cattaneo, S. Antinori, M. Galli, Early administration of lopinavir/ritonavir plus hydroxychloroquine does not alter the clinical course of SARS-CoV-2 infection: a retrospective cohort study, J. Med. Virol. 93 (3) (2021) 1421–1427.

[2] S. Antinori, M.V. Cossu, A.L. Ridolfo, R. Rech, C. Bonazzetti, G. Pagani, G. Gubertini, M. Coen, C. Magni, A. Castelli, B. Borghi, R. Colombo, R. Giorgi, E. Angeli, D. Mileto, L. Milazzo, S. Vimercati, M. Pellicciotta, M. Corbellino, A. Torre, S. Rusconi, L. Oreni, M.R. Gismondo, A. Giacomelli, L. Meroni, G. Rizzardini, M. Galli, 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, Pharmacol. Res. 158 (2020), 104899.

[3] J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W. R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, H.C. Lane, ACTT-1 study group members. remdesivir for the treatment of Covid-19 – final report, N. Engl. J. Med. 383 (19) (2020) 1813–1826.

[4] Y. Wang, D. Zhang, G. Du, R. Du, J. Zhao, Y. Jin, S. Fu, L. Gao, Z. Cheng, Q. Lu, Y. Hu, G. Luo, K. Wang, Y. Lu, H. Li, S. Wang, S. Ruan, C. Yang, C. Mei, Y. Wang, D. Ding, F. Wu, X. Tang, X. Ye, Y. Ye, B. Liu, J. Yang, W. Yin, A. Wang, G. Fan, F. Zhou, Z. Liu, X. Gu, J. Xu, L. Shang, Y. Zhang, L. Cao, T. Guo, Y. Wan, H. Qin, Y. Jiang, T. Jaki, F.G. Hayden, P.W. Horby, B. Cao, C. Wang, Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial, Lancet 395 (10236) (2020) 1569–1578.

[5] ⟨https://www.aifa.gov.it/documents/20142/1123276/remdesivir_update01_24.11.2020.pdf⟩. (Accessed 21 May 2021).

[6] B.N. Williamson, F. Feldmann, B. Schwarz, K. Meade-White, D.P. Porter, J. Schulz, N. van Doremalen, I. Leighton, C.K. Yinda, L. Pérez-Pérez, A. Okumura, J. Lovaglio, P.W. Hanley, G. Saturday, C.M. Bosio, S. Anzick, K. Barbian, T. Cihlar, C. Martens, D. P. Scott, V.J. Munster, E. de Wit, Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2, Nature 585 (2020) 273–276.

[7] A. Giacomelli, A.L. Ridolfo, L. Milazzo, L. Oreni, D. Bernacchia, M. Siano, C. Bonazzetti, A. Covizzi, M. Schiuma, M. Passerini, M. Piscaglia, M. Coen, G. Gubertini, G. Rizzardini, C. Cogliati, A.M. Brambilla, R. Colombo, A. Castelli, R. Rech, A. Riva, A. Torre, L. Meroni, S. Rusconi, S. Antinori, M. Galli, 30-day mortality in patients hospitalized with COVID-19 during the first wave of the Italian epidemic: a prospective cohort study, Pharmacol. Res. 158 (2020), 104931.

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