Bradycardia during remdesivir treatment might be associated with improved survival in patients with COVID-19: a retrospective cohort study on 473 patients from a tertiary centre

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Remdesivir is the only antiviral drug currently approved for the treatment of severe COVID-19. It was recently observed that use of remdesivir might be associated with higher frequency of transitory bradycardia,1,4 a phenomenon that was reported in 19%–47% of remdesivir-treated patients without clear clinical significance. Since a number of other potentially detrimental cardiovascular adverse events were reported with remdesivir use,5 understanding clinical consequences of these phenomena is of utmost importance in everyday clinical practice.

We have retrospectively investigated a cohort of 473 patients with COVID-19 hospitalised in a tertiary-level institution in period from September 2020 to April 2021 who received remdesivir. All patients were concurrently requiring oxygen supplementation therapy and were treated with corticosteroids and low-molecular weight heparin. All patients were Caucasian. Remdesivir was given for 5 days in 455 (96.2%) and longer in 18 (3.8%) patients. Data on patient demographic and clinical parameters are a part of hospital registry project and were obtained through analysis of written and electronic medical records. Heart rate was assessed before, during each day of remdesivir treatment and 5 days after discontinuation of therapy. COVID-19 severity on admission was defined by the WHO guidelines. Normality of distribution of numerical variables was tested using the Shapiro-Wilk test. Numerical variables did not follow normal distribution and were presented as median and IQR and compared between groups using the Mann-Whitney U test. Categorical variables were presented as frequencies and percentages and were compared between groups using the \( \chi^2 \) test. Logistic regression was used to assess odds ratios (OR) for different clinical outcomes associated with bradycardia occurrence. P values <0.05 were considered statistically significant. All analyses were done using the MedCalc statistical software V.20.008 (MedCalc Software, Ostend, Belgium).

Median age was 65 years IQR (56–72.3). A total of 312 (66%) patients were men, 53 (11.2%) had atrial fibrillation (AF) and 141 (29.8%) used beta blockers (BB), respectively. Median Charlson Comorbidity Index (CCI) was 3 IQR.2,4 Median C reactive protein and interleukin-6 levels on admission were 110.7 mg/L and 44.2 pg/mL, respectively. During hospital stay 175 (37%) patients required high-flow oxygen therapy (HFOT), 131 (27.7%) mechanical ventilation and 162 (34.2%) intensive care unit treatment (ICU), respectively. A total of 136 (28.8%) patients died.

Bradycardia (heart rate <60 beats/min) was present in only 1.3% patients before remdesivir treatment. The rate of bradycardia steadily increased up to 5th day of treatment (6.6%, 12.6%, 15.4% and 16.8% patients experienced bradycardia at the day 2, 3, 4 and 5 of therapy, respectively) and subsequently diminished (15%, 15.6%, 15.2%, 12.7% and 11.8% patients experienced bradycardia at the day 1, 2, 3, 4 and 5 post-treatment, respectively; figure 1A). There were no significant differences in neither age, sex, CCI, COVID-19 severity on admission, AF, BB use, inflammatory parameters on admission, body temperature on admission, body temperature on 5th day of remdesivir treatment nor occurrence of bacterial sepsis during hospitalisation between patients with and without day 5 bradycardia occurrence (p>0.05 for all analyses). Lowest recorded heart rate on day 5 of remdesivir treatment was 35/min in a patient with AF difficult to rate control who required sedation due to mechanical ventilation and who subsequently died. When stratifying patients according to the outcome of hospitalisation (figure 1B), similar pattern of bradycardia occurrence could be observed in both patients who died and who were discharged alive from the hospital (gradual increase during remdesivir use with subsequent decrease). However, the occurrence of bradycardia was more pronounced among surviving patients. Statistically significantly higher rates of bradycardia in surviving versus dying patients could be demonstrated for day 5 of remdesivir treatment (19.2% vs 7.3%; p=0.010), day 1 post-treatment (17% vs 7.1%; p=0.039) and day 4 post-treatment (15.1% vs 5.1%; p=0.044). Occurrence of bradycardia on day 5 of remdesivir treatment was significantly associated with lower odds for death during hospitalisation (OR 0.33 (95% CI 0.14 to 0.79); p=0.014), HFOT use (OR 0.33 (95% CI 0.16 to 0.7); p=0.004) and ICU stay (OR 0.43 (95% CI 0.2 to 0.91); p=0.027). In the multivariate logistic regression analysis, absence of remdesivir day 5 bradycardia occurrence (OR 0.39; p=0.043), more severe COVID-19 on admission...
Our results demonstrate that bradycardia occurring during remdesivir use might reflect more favourable disease course and has a substantial potential for improving prognostication of patients with COVID-19. Frequency of bradycardia in our cohort (16.8%) was lower than previously reported in smaller patient cohorts (19%–47%)2–4 which could be attributed to differences in baseline age, sex and comorbidity profile of patients. Underlying mechanisms behind bradycardia temporarily associated with the administration of remdesivir remain elusive at the moment. Nevertheless, patients with tendency for respiratory deterioration experiencing poor clinical outcomes seem to be less responsive to these mechanisms, possibly due to stronger sympathetic-adrenergic stimulation. Thus, experiencing remdesivir-associated bradycardia, the most frequent cardiovascular side effect of the drug, seems to be a sign of good prognosis and should encourage physicians to rather continue than discontinue the drug with intensified measures of patient surveillance. Surveillances are especially important for real-life patients with high comorbidity burden that often do not fit into original clinical trial criteria and might require synchronous treatment for other medical conditions. Very low heart rates and fatal outcomes are possible (unknown whether causally related to remdesivir). Studies determining real-life efficacy and safety of remdesivir for the treatment of COVID-19 have shown varying results. In the absence of uniform evidence of clinical benefit, the proper role of remdesivir and the target group of patients are yet to be determined.

Main limitations of our work are single-centre experience and retrospective study design. Main strengths of our work are data based on a uniformly treated cohort of real-life patients and large sample size representative of tertiary centre experience.

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