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Research note

A real-life setting evaluation of the effect of remdesivir on viral load in COVID-19 patients admitted to a large tertiary centre in Israel

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ABSTRACT

Objectives: The effectiveness of remdesivir, a Food and Drug Administration-approved drug for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has been repeatedly questioned during the current coronavirus disease 2019 (COVID-19) pandemic. Most of the recently reported studies were randomized controlled multicentre clinical trials. Our goal was to test the efficiency of remdesivir in reducing nasopharyngeal viral load and hospitalization length in a real-life setting in patients admitted to a large tertiary centre in Israel.

Methods: A total of 142 COVID-19 patients found to have at least three reported SARS-CoV-2 quantitative RT-PCR tests during hospitalization were selected for this study. Of these, 29 patients received remdesivir, while the remaining non-treated 113 patients served as controls.

Results: Among the tested parameters, the control and remdesivir groups differed significantly only in the intubation rates. Remdesivir treatment did not significantly affect nasopharyngeal viral load, as determined by comparing the differences between the first and last cycle threshold values of the SARS-CoV-2 quantitative RT-PCR tests performed during hospitalization (cycle threshold 7.07 ± 6.85 vs. 7.08 ± 7.27, p 0.977 in the control and treated groups, respectively). Remdesivir treatment shortened hospitalization length by less than a day compared with non-treated controls and by 3.1 days when non-intubated patients from both groups were compared. These differences, however, were not statistically significant, possibly because of the small size of the remdesivir group.

Discussion: Remdesivir was not associated with nasopharyngeal viral load changes, but our study had a significant disease severity baseline imbalance and was not powered to detect viral load or clinical differences. **Elad Goldberg, Clin Microbiol Infect 2021;27:917.e1–917.e4**

Introduction

The rapid spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and its high burden on health systems have led to a global effort to identify drugs that may reduce morbidity and mortality [1]. Testing previously identified drugs for their efficiency in reducing SARS-CoV-2 replication is a straightforward avenue for timely antiviral therapy implementation.

Remdesivir is a prodrug converted to an adenosine nucleoside triphosphate analogue. This analogue acts as an irreversible chain terminator, blocking transcription by the viral RNA polymerase [2]. Remdesivir demonstrated SARS-CoV-2 antiviral activity both *in vitro* and *in vivo* [3,4]. Clinical trials, however, were inconclusive or showed limited efficiency [5]. The WHO open-label randomized Solidarity trial interim results did not show any significant effect of remdesivir on any tested parameter [6]. However, the Adaptive

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COVID-19 Treatment Trial (ACTT-1) showed that remdesivir was superior to placebo in shortening the time to recovery in non-intubated patients [7]. Here we aimed to test the potential of remdesivir to reduce viral replication, as assessed by repeated nasopharyngeal PCR tests, in a real-life setting.

Methods

COVID-19 patients (n = 142, females 40.47%, median age 70 years (IQR 59–80.75)), admitted to the coronavirus ward at Rabin Medical Center between March and November 2020, who had at least three nasopharyngeal SARS-CoV-2 quantitative RT-PCR tests during hospitalization, were included. Of these, 29 patients received remdesivir, based on disease severity and time from onset of symptoms, while the remaining 113 non-treated patients served as controls. For baseline demographics see supplementary tables 1 and 2. Treated patients received intravenous remdesivir (200 mg on day 1, followed by 100 mg on days 2–5 in single daily infusions). The study was approved by the institutional review board (0252-20-RMC) and the Tel-Aviv university ethics committee (0001269-3). Test results and demographic data were collected from the patients' medical records. Cycle threshold (Ct) values of the nucleocapsid gene were used to assess the viral loads. RT-PCR was performed using the Allplex™ 2019-nCoV Assay (Seegene). To test the effect of remdesivir on nasopharyngeal viral load, we calculated the differences in Ct values (Δ) between patients' tests. Student's t-tests for two independent samples were applied to test the difference between treatment groups. Analysis of covariance (ANCOVA) was applied to adjust these comparisons to age, gender and intubation (yes/no). A linear model for repeated measures was performed for testing the statistical significance of the difference in changes across the three tests, adjusted to the parameters mentioned above. Chi-squared tests were applied for testing the statistical significance of the difference in the binary variable increase/decrease between treatment groups. Logistic regressions were applied to adjust these comparisons to the parameters mentioned above. The data were analysed using SAS® v. 9.4 or GraphPad Prism.

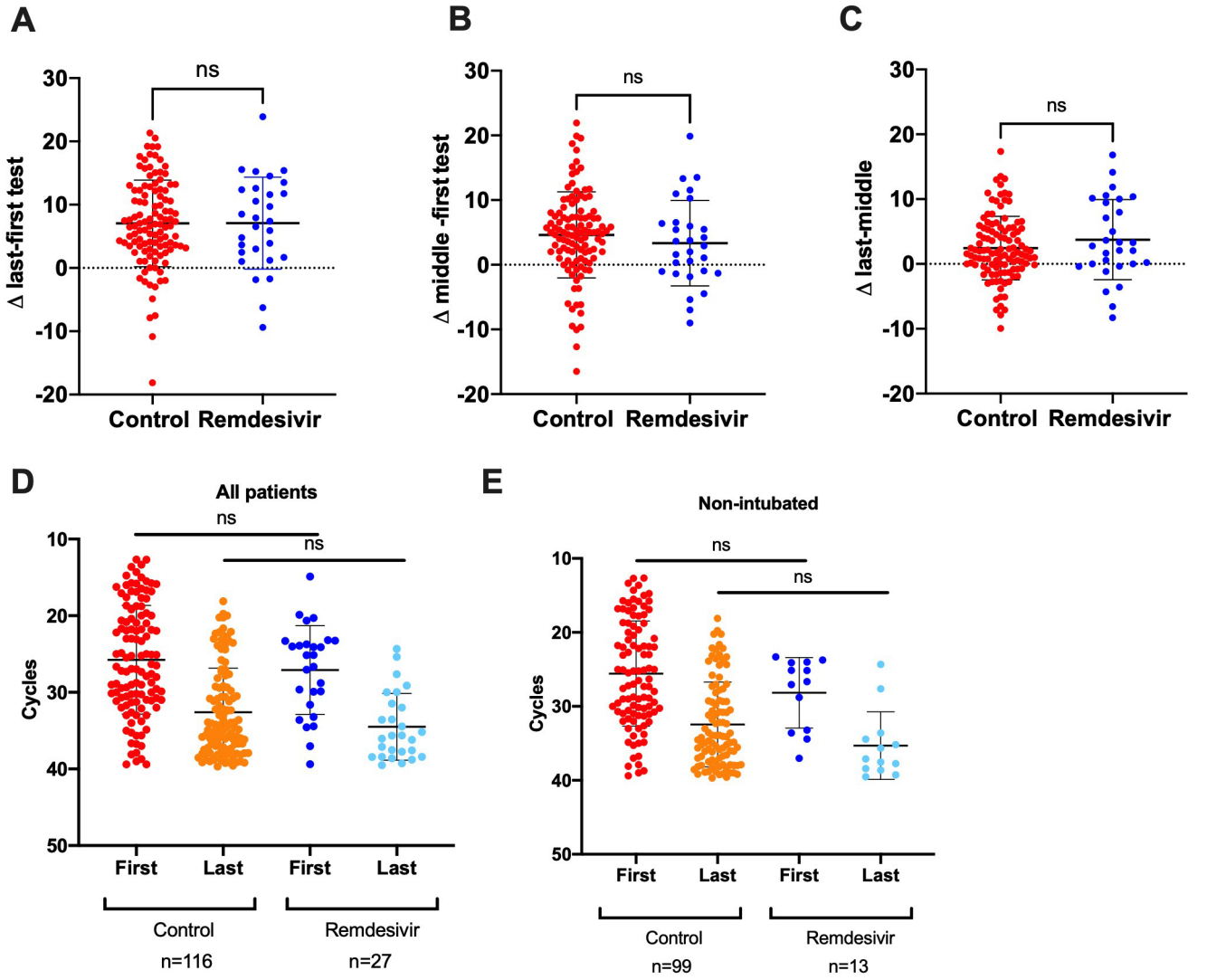

Fig. 1. Ct values from control and remdesivir-treated patients. First, middle and last Ct values (A,B,C, respectively) from the nucleocapsid gene from control and remdesivir treated patients were compared (n = 142). The difference (Δ) between the indicated test Ct values is shown (A, B, C, p 0.977, p 0.362, p 0.228, respectively, unpaired Student's t-test). The Ct values of the first and last test in the control or remdesivir-treated patients are shown both for all patients (D, first p 0.365, last p 0.109, unpaired Student's t-test) or non-intubated patients only (E, first p 0.203, last p 0.088, unpaired Student's t-test). ns, non-significant.

Results

The average number of tests was 5.34 ± 2.67 in the control vs. 4 ± 1.7 in the remdesivir group. The differences in Ct values (Δ) between patients' first and last tests were calculated (Fig. 1A). Overall, ~128-fold reduction in viral load was detected in both the control and the treated patients, with no significant difference between the groups (Ct 7.07 ± 6.85 vs. 7.08 ± 7.27, p 0.977). Since some of those patients were admitted for extended periods (maximal hospitalization length = 55 days), we performed the same analysis on the first and middle tests (Fig. 1B) and the middle and last tests (Fig. 1C). No detectable differences were noted (4.6 ± 6.65 vs. 3.34 ± 6.59, p 0.362 and 2.44 ± 4.9 vs. 3.74 ± 6.18, p 0.228, respectively). Since our study was retrospective, we verified that the average test intervals were similar between the control and remdesivir groups (7.14 ± 6.16 and 7.07 ± 5.52 respectively, p 0.923, student's *t*-test). The control and remdesivir groups significantly differed only in the intubation rates (12.4 vs. 41.4% respectively p 0.0003), thus these comparisons were further adjusted to age, gender and intubation status using ANCOVA. The corrected means showed no significant differences from the original analysis (first to last, p 0.768; first to middle, p 0.94; middle to last, p 0.504). In addition, a linear model for repeated measures was performed to test the statistical significance of the difference in changes across the three tests, adjusted to the parameters mentioned above, between treatment groups. To further verify the results, we converted the numerical values of the differences across the tests into dichotomous values (increase/decrease). Chi-squared tests were applied for testing the statistical significance of the difference in the viral load between treatment groups (first to last, decreasing 11.5% vs. 13.8%, p 0.7349; first to middle, 17.7% vs. 31%, p 0.112, middle to last, 29.2% vs. 24.1%, p 0.588). Logistic regressions were applied to adjust these comparisons to age, gender and intubation (first to last, p 0.418; first to middle; p 0.696, middle to last p 0.7831). Of note, remdesivir-treated patients had slightly lower viral loads than non-treated controls on their first test; this difference, however, was not significant (26.8 ± 7.05 vs. 25.67 ± 6.02, p 0.365, Fig. 1D). This difference remained non-significant when the last tests of both groups were compared (33.94 ± 5.22 vs. 32.54 ± 5.78, p 0.109). Since some studies suggested that remdesivir is only efficient for individuals diagnosed early and required oxygen supplementation [8], an additional analysis comparing the Ct values between non-intubated treated and untreated patients was performed. Ct values were similar between these groups at their first test (27.74 ± 4.76 vs. 25.67 ± 7.1, p 0.2034, Fig. 1E). Ct values remained similar when each patient's last test was compared (34.4 ± 4.78 vs. 32.58 ± 5.76, p 0.0885). Remdesivir was previously reported to reduce time to recovery, defined by time from admission to discharge [7]. Thus, to measure hospitalization length, we tested the time from the first test to discharge (deceased patients were excluded from this analysis). Analysis of the whole cohort indicated that remdesivir reduced hospitalization by 1.4 days (15.3 ± 11.4 vs. 13.9 ± 9.2, p 0.769, Fig. 2A). When only non-intubated patients were analysed, hospitalization was reduced by 3.1 days (14.2 ± 10 vs. 11.1 ± 5.4, p 0.3, Fig. 2B). These differences, however, were not statistically significant.

Discussion

Only patients with severe disease requiring oxygen support were eligible for remdesivir treatment. There were no clear WHO recommendations until November 2020. Currently, WHO does not recommend remdesivir. While nasopharyngeal viral load is not an established marker for therapeutic effect in hospitalized COVID-19 patients, nasopharyngeal swab Ct values were shown to correlate with infectious virus and clinical outcome [9–12]. Our results indicate that remdesivir treatment of COVID-19 patients did not significantly reduce nasopharyngeal viral load. These results are in line with results from a macaque experiment, showing that remdesivir reduced viral load in the lower but not the upper respiratory tract [13]. In contrast, a clinical study by Wang et al. could not detect any effect of remdesivir on viral load, in neither the upper nor lower respiratory tracts [14]. Our study has the advantage of testing remdesivir efficacy in patients in a real-life setting. However, the lack of PCR tests from the lower respiratory tract in our cohort cannot rule out a possible antiviral effect in the lower respiratory tract.

Hospitalization length was reduced by 1 day when the whole patient cohort was analysed. A more considerable but not

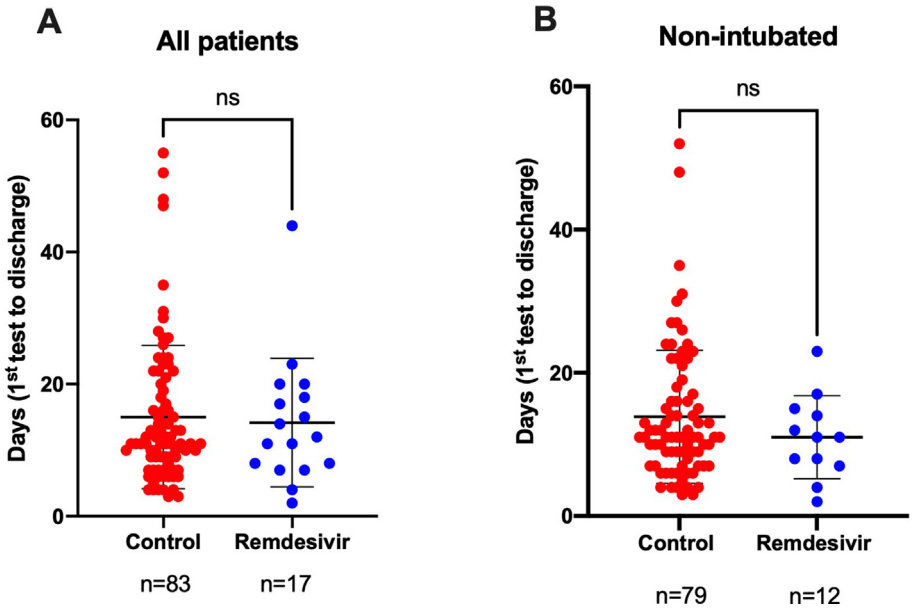

Fig. 2. Hospitalization length in remdesivir treated patients and controls. Time in days from the first recorded test to discharge in all control and remdesivir-treated patients (A, p 0.769, unpaired Student's *t*-test) or non-intubated patients only (B, p 0.3, unpaired Student's *t*-test).

statistically significant reduction of ~3.1 days was observed in the non-intubated group. Despite the relatively small size of our cohort, these real-life results are in agreement with the ACTT-1 trial, showing a modest effect of remdesivir only in non-intubated patients [7]. Our study limitations are its retrospective nature, which did not allow sampling at regular intervals, and its small sample size. Our results call for real-life higher-powered studies to further evaluate a possible clinical benefit of remdesivir.

Transparency declaration

The authors declare that they have no conflicts of interest.

Author contributions

E.G. and E.H.S. conceptualized the study and its methodology. H.B.Z., L.S. and S.S. collected and analysed the data. I.K., A.S., E.G., and E.H.S. wrote the first draft. All authors reviewed and edited the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.02.029.

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