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LETTER TO THE EDITOR

Liver injury in remdesivir-treated COVID-19 patients

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Novel Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) infection results predominantly in pulmonary involvement (Coronavirus disease 2019, COVID-19), but a direct, SARS-CoV-2-induced liver damage has also been described [1, 2]. Thus, it is important to monitor liver function and evaluate hepatic safety of drugs administered to COVID-19 patients. Remdesivir (RDV), a nucleotide analogue RNA polymerase inhibitor, originally developed and tested for Ebola virus disease, showed in vitro efficacy against SARS-CoV-2 [3], and experience on its efficacy and safety for COVID-19 is accumulating [4, 5]. However, hepatic safety of RDV in COVID-19 has not been the focus of detailed investigation. Here, we describe patterns of liver toxicity in 5 COVID-19 patients treated with RDV in the intensive care unit (ICU) of Monaldi Hospital, Naples, Italy, during March and April 2020. Overall, our Hospital cared for 32 critically ill COVID-19 patients.

Treatment was given in a compassionate use program (CPU) approved by our Ethics Committee. CPU was limited to the first 5 patients of our center who fulfilled all eligibility criteria (invasive mechanical ventilation, no multiorgan failure, no vasopressor requirement, ALT levels < 5 xULN, creatinine clearance > 30 mL/min). RDV was administered intravenously as a 200 mg loading dose, followed by 100 mg daily over 1 h for up to 9 days. According to the early recommendations of the Italian Society for Infectious Diseases, Lombardy section, all patients had been previously treated with lopinavir/ritonavir (LPV/r, 400/100 mg twice daily po). Before and during RDV treatment, 4 of 5 patients also received hydroxychloroquine (HCQ, 200 mg twice daily po). While on RDV, no patient received acetaminophen, patient 2 and 4 received ceftazidime–avibactam plus daptomycin and patient 3 meropenem and linezolid. None of the 5 treated patients had a previous history of liver disease, visceral obesity, viral hepatitis, or prior hepatotoxic medication or alcohol intake. Liver ultrasound did not show signs of advanced liver disease. Patient 1 and 2 had a history of hypertension and asthma, respectively, but were not receiving any relevant therapy in the ICU.

Figure 1 describes the dynamics of AST/ALT and bilirubin throughout the hospital stay, for each patient (Panels 1–5). In Panel 6, we report a comparison of median ALT and AST levels between RDV-treated patients and 5 COVID-19 patients who were treated in our Hospital ICU with the same schedule of LPV/r and HCQ, but without RDV. As shown in Panels 1–5, bilirubin increase occurred in 4 of 5 index patients on LPV/r. In contrast, the switch to RDV translated into a fast reduction of bilirubin and a significant increase in AST/ALT by day 3 of therapy in 4 of 5 patients. The single patient who did not receive HCQ with RDV (patient 4) did not show increase of ALT/AST levels. In no cases, RDV was discontinued because of liver injury. In patient 1, RDV was withdrawn at day 5 for a torsade de pointes requiring cardiac resuscitation, whereas patient 3 died on day 5 of RDV therapy. Final outcome was positive in 4/5 patients.

Our observation supports previous findings obtained in healthy volunteers (Gilead Sciences, data on file) and COVID-19 patients treated with RDV [4, 5], suggesting this antiviral may cause hepatocellular injury. In our patients, this adverse effect neither progressed to severe liver damage nor induced liver failure, although none had a prior chronic liver disease. Although SARS-CoV-2 infection can cause aminotransferase elevation per se, 4 of our 5 patients had normal or slightly elevated AST/ALT levels at RDV treatment start, suggesting a direct role of RDV in hepatocellular toxicity. Despite the overall low number of patients

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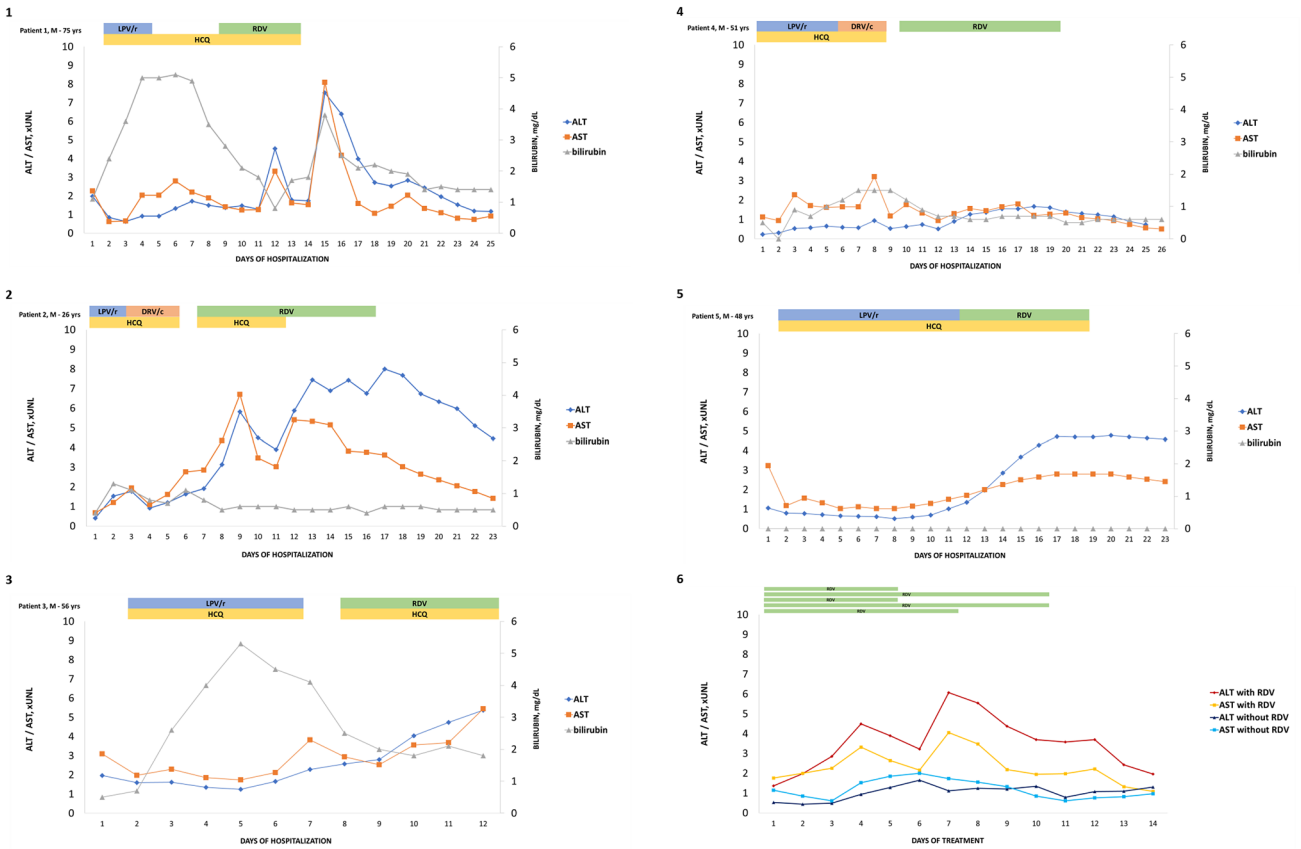

Fig. 1 Dynamics of ALT, AST and bilirubin in the 5 patients treated with Remdesivir (Panels 1–5). Aminotransferase values are shown as times the upper normal limit. Antivirals given are shown on top of each graph. Panel 6 shows a comparison of median ALT and AST levels between the 5 RDV-treated patients and 5 additional COVID-19 patients who were treated in our Hospital ICU with the same schedule of LPV/r and HCQ but without RDV. *LPV/r* lopinavir/ritonavir, *DRV/c* darunavir/cobicistat, *HCQ* hydroxychloroquine, *RDV* remdesivir, *UNL* upper normal limit

treated, we observed a clear trend of bilirubin elevation with LPV/r and ALT/AST elevation with RDV. Our observation suggests RDV can be used with close monitoring of liver function tests and with caution in subjects with prior liver disease.

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Compliance with ethical standards

Conflicts of interest The authors declared that they have no conflict of interest.

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