Caution With the Use of Lopinavir/Ritonavir in Severely Ill Patients for the Treatment of SARS-CoV-2: A Report of Severe Jaundice

Clementine Levy, MD1, Guillaume Lassailly, MD2, Erika Parmentier, MD1, Thibault Duburcq, MD1, Philippe Mathurin, MD, PhD2 and Julien Poissy, MD, PhD1

INTRODUCTION: We investigated the potential hepatotoxicity of lopinavir/ritonavir recently used in the treatment of Severe Acute Respiratory Syndrome Coronavirus.

METHODS: This is a retrospective cohort of critical patients in a teaching hospital: 12 treated with lopinavir/ritonavir and 30 in the standard-of-care group.

RESULTS: Elevation occurred more frequently in patients treated with lopinavir/ritonavir (33% vs 6.7%).

DISCUSSION: Caution is advised regarding the use of lopinavir/ritonavir in the most severe cases of Severe Acute Respiratory Syndrome Coronavirus.
admission with a ratio between partial pressure of oxygen and fraction of inspired oxygen (PaO2/FiO2) of 142 mm Hg. The group of patients treated with lopinavir/ritonavir was more severe at admission with Simplified Acute Physiology Score II of 49.5 (36–60) vs 35.5 (24–53.5), \( P = 0.011 \). Albumin (23 g/L [21–26] vs 30 g/L [25–35] \( P = 0.006 \)) and prothrombin time (73% [62–79] vs 85% [69–92] \( P = 0.026 \)) were also significantly lower. C-reactive protein (205 [102–285] vs 150 [62–234] \( P = 0.38 \)), leukocytes (7 G/L [5.6–10.5] vs 6.9 G/L [6.7–8.5] \( P = 0.94 \)), and total bilirubin (0.6 [0.4–0.8] vs 0.6 [0.4–0.9] \( P = 0.67 \)) were similar at admission between the groups. None of the patient underwent renal replacement therapy (RRT) at admission or had a history of cirrhosis in the 2 groups. All characteristics at baseline are detailed in Table 1.

During the follow-up, 33% of patients in the lopinavir/ritonavir group had an increase of bilirubin or jaundice vs 6.7% \( (P = 0.046) \) in the standard care group. Total bilirubin increased in the lopinavir/ritonavir group from the first to the seventh day and was significantly higher during this period as compared to the standard care group in which the total bilirubin level remains stable (Figure 1.). Transaminases levels over time were not significantly different between the 2 groups.

Of our 12 patients treated with lopinavir/ritonavir, 6 died in the lopinavir/ritonavir group (3 multiorgan failure, 1 cardiac arrest, and 2 withdrawal of care) and 4 died in the standard care group (3 withdrawal of care and 1 cardiac arrest). There was no case of acute liver failure.

Kidney function and RRT recourse did not differ between the 2 groups. Extraorporeal membrane oxygenation (ECMO) was used in 2 patients in the lopinavir/ritonavir group vs 1 in the standard care group.

Finally, in the lopinavir/ritonavir group, liver adverse events were classified as serious in 2 cases with grade 3–4 and not severe in 2 cases with grade 1–2. Among these 4 patients, 3 returned to baseline bilirubin between 2 and 10 days after treatment withdrawal. The last patient did not recover from jaundice, required ECMO, and died of multiorgan failure. Death was not related to acute liver failure.

**DISCUSSION**

Before the use of lopinavir/ritonavir in the setting of COVID-19, liver toxicity, mostly elevated liver enzymes without jaundice, nor acute liver failure have been described in the human immunodeficiency virus population. This liver toxicity is preferentially observed in patients coinfected with hepatitis C with pre-existing abnormal liver test at the introduction of lopinavir/ritonavir (5,6). We now report elevated total bilirubin during lopinavir/ritonavir treatment.

Jaundice or elevation of total bilirubin occurred more frequently (33%) in our COVID-19 patients treated with lopinavir/ritonavir.

**Table 1. Characteristics at ICU admissions of lopinavir/ritonavir and standard of care patients**

| Characteristics at ICU admission | Lopinavir/ritonavir N = 12 | Standard care N = 30 | \( P \) Value |
|---------------------------------|-----------------------------|---------------------|-------------|
| Age, median (95% CI)            | 61 (54–73)                  | 64 (53–69)          | 0.86        |
| BMI, median (95% CI)            | 30 (28–38)                  | 31 (28–33)          | 0.95        |
| Gender (male, %)                | 58.3                        | 66.7                | 0.61        |
| SAPS-II                         | 49.5 (37–59)                | 35.5 (29–47)        | 0.011       |
| Arterial hypertension (%)       | 33.3                        | 46.7                | 0.62        |
| Diabetes (%)                    | 8.3                         | 36.7                | 0.13        |
| Chronic kidney failure (%)      | 8.3                         | 13.3                | 0.65        |
| Mechanical ventilation          | 58.3                        | 26.7                | 0.08        |
| PaO2/FiO2, median               | 142 (94–218)                | 142 (100–182)       | 0.57        |
| Vasopressor (%)                 | 25                           | 23.3                | 0.90        |
| Heart failure (%)               | 8.3                         | 6.7                 | 0.85        |
| Leukocytes, median G/L          | 7 (5.6–10.5)                | 6.9 (6.7–8.5)       | 0.94        |
| Platelets, median G/L           | 168 (109–236)               | 187 (170–203)       | 0.41        |
| Total bilirubin, median mg/dL   | 0.6 (0.5–0.7)               | 0.6 (0.5–0.6)       | 0.67        |
| Arterial lactate (mmol/L)       | 1.25 (1–1.5)                | 1.45                | 0.88        |
| Creatinine mg/dL                | 0.8 (0.7–1.3)               | 0.85 (0.7–0.9)      | 0.95        |
| Albumin, g/L                    | 23 (21–26)                  | 30 (29–32)          | 0.006       |
| AST, IU/L                       | 59 (45–104)                 | 58 (50–61)          | 0.70        |
| ALT, IU/L                       | 82 (48–98)                  | 37 (35–50)          | 0.07        |
| Prothrombin time (%)            | 73 (64–77)                  | 85 (80–89)          | 0.026       |
| CRP (mg/L)                      | 205 (102–285)               | 150 (62–234)        | 0.38        |

BMI: body mass index; CRP: C-reactive protein; ICU, intensive care unit; SAPS II, Simplified Acute Physiology Score II.
ritonavir, whereas a recent trial did not show difference in bilirubin between the lopinavir/ritonavir and standard care groups. The accountability of lopinavir/ritonavir in the elevation of bilirubin has also been reported in a cohort of 417 COVID-19 patients (7). These discrepancies in liver adverse events between our experience and the results from randomized controlled trial may be related at least in part to differences in baseline disease severity and host factors. The frequency of elevated bilirubin in our standard group (6.7%) was higher than that in the study of Cao et al. (3.2% in the lopinavir/ritonavir group and 3% in the control group). Only one patient requiring mechanical ventilation was included in this trial that recruited patients suffering from mild disease. Our patients treated with lopinavir/ritonavir were more severe: all were admitted to intensive care, 58% required mechanical ventilation, 33% RRT, and 16% ECMO. Hypoalbuminemia, frequently observed (71%) in our patients, might have altered pharmacokinetics of lopinavir/ritonavir favoring overexposure, whereas less than 1% of patients from the RCTs had hypoalbuminemia. In the same way, the major inflammatory syndrome, as suggested by the levels of C-reactive protein, and potential mitochondrial dysfunction (8) could also have impaired the drug metabolism. Underlying liver steatosis might also be a contributing factor of liver toxicity of lopinavir/ritonavir because 60% of our patients were obese (9).

Thus, close monitoring, dosage of lopinavir/ritonavir, and dose adjustment should be proposed in clinical trials including critically ill patients in whom lopinavir/ritonavir could be less tolerated than in noncritically ill patients. Caution is advised regarding the widespread use of lopinavir/ritonavir in severely ill patients in ICUs, in whom liver function should be closely monitored.

CONFLICTS OF INTEREST
Guarantor of the article: Clementine Levy, MD.
Specific author contributions: C.L.: conducted the study, drafted the manuscript, and collected the data. G.L.: conducted the study, drafted the manuscript, and interpreted the data. E.P.: collected and interpreted the data. T.D.: collected and interpreted the data and drafted the manuscript. P.M.: drafted the manuscript. J.P.: conducted the study and drafted the manuscript
Financial support: None to report.
Potential competing interests: None to report.

REFERENCES
1. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: Initial virological and clinical findings. Thorax 2004;59(3):252–6.
2. Wong JF-W, Yao Y, Yeung M-L, et al. Treatment with lopinavir/ritonavir or interferon-beta1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. J Infect Dis 2015;212(12):1904–13.
3. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11(1):222.
4. Cao B, Wang Y, Wen D, et al. A trial of lopinavir/ritonavir in adults hospitalized with severe covid-19. N Engl J Med 2020;382(19):1787–99.
5. Canta F, Marrone R, Bonora S, et al. Pharmacokinetics and hepatotoxicity of lopinavir/ritonavir in non-cirrhotic HIV and hepatitis C virus (HCV) co-infected patients. J Antimicrob Chemother 2005;55(2):280–1.
6. Palacios R, Vergara S, Rivero A, et al. Low incidence of severe liver events in HIV patients with and without hepatitis C or B coinfection receiving lopinavir/ritonavir. HIV Clin Trials 2006;7(6):319–23.
7. Cai Q, Huang D, Yu H, et al. COVID-19: Abnormal liver function tests. J Hepatol 2020.
8. Shi CS, Nabar NR, Huang NN, et al. SARS-coronavirus open reading frame-8b triggers intracellular stress pathways and activates NLRP3 inflammasomes. Cell Death Discov 2019;5:101.
9. Allard J, Le Guillou D, Fromenty B, et al. Drug-induced liver injury in obesity and nonalcoholic fatty liver disease. Adv Pharmacol 2019;85:75–107.