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Lopinavir and low-dose ritonavir (LPV/RTV) are associated in a fixed-dose combination protease inhibitor therapy used in patients with HIV and AIDS. The recent outbreak of severe acute respiratory syndrome coronavirus 2 infections causing coronavirus disease 2019 (COVID-19) has rekindled the interest in LPV/RTV after preclinical studies.[1] Although no benefit was observed with LPV/RTV treatment beyond standard care,[2] other randomized controlled trials, such as DisCoVeRy (NCT04315948), are currently enrolling. Like other antiretroviral therapies, LPV/RTV has been previously associated with acute kidney injuries (AKIs), even though no systematic pharmacovigilance analysis was ever performed.

We first describe a small case series of AKI associated with LPV/RTV in the course of COVID-19 treatment. We then performed a query in the World Health Organization pharmacovigilance database, VigiBase, and extracted all AKIs associated with LPV/RTV. We then presented clinical characteristics of these events and performed a comparison between HIV and COVID-19 indication in VigiBase.

METHODS

Study Design

This work combines a case series of all patients who presented with AKI under LPV/RTV in our intensive care medicine department and a worldwide pharmacovigilance observational case-control cross-sectional study focusing on AKI related to the usage of LPV/RTV. It relies on VigiBase, a database encompassing 22 million individual case safety reports worldwide.[3] Individual case safety reports include administrative information, the drug involved, patient data, date of onset, and nature of the outcome using the Medical Dictionary for Regulatory Activities terms (version 22.1). This work is ancillary to the Adverse Events Related to Treatments Used Against Coronavirus Disease 2019 (ClinicalTrials.gov identifier NCT04314817).

Analyses in VigiBase

To confirm whether LPV/RTV was significantly associated with AKI overreporting in VigiBase, we performed a disproportionality analysis also known as case–noncase analysis, following a methodology that our group, like others, previously described.[4] Included cases were individual case safety reports with LPV/RTV suspected to be associated with AKI, flagged using the Medical Dictionary for Regulatory Activities preferred term level "acute kidney injury" from inception to May 10, 2020 (see Supplementary Table 1 for details on the chosen preferred term level). The computed Bayesian disproportionality estimate was the information component (IC). The IC_{025} is the lower end of the 95% credibility interval for the IC. A positive value of the IC_{025} is significant.[5] More information concerning calculation of the IC and IC_{025} are provided in the Supplementary Material.

Continuous data were reported as median (interquartile range [IQR]) because of their nonnormal distribution, and when applicable group comparisons

Table 1. Clinical summary of patients treated with lopinavir and low-dose ritonavir for COVID-19 who presented with acute kidney injuries

Patient no.	Sex	Age, yr	SOFA score	Vasopressor agent	KDIGO classification	Dialysis required?	Chronic kidney disease	Time to onset, d	Death	Proteinuria	Hematuria	Lactic acidosis
#1	M	41	3	Yes	2	Yes	No	3	Yes	Yes	No	No
#2	F	70	11	Yes	2	No	No	0	No	No	No	No
#3	M	81	9	Yes	3	No	No	1	Yes	Yes	Yes	No
#4	F	70	5	Yes	3	No	No	0	Yes	Yes	Yes	No
#5	M	54	9	No	3	No	No	0	No	Yes	Yes	No
#6	M	78	5	Yes	3	Yes	No	0	Yes	Yes	Yes	No
#7	F	55	4	Yes	2	No	No	1	No	Yes	No	No
#8	M	63	12	Yes	2	No	No	0	No	No	Yes	No

COVID-19, coronavirus disease 2019; F, female; KDIGO, Kidney Disease Improving Global Outcomes; M, male; SOFA, Sequential Organ Failure Assessment.

were performed using nonparametric tests. Time to onset was computed as the time in days between the initiation of LPV/RTV and the date of AKI. Concurrent renal adverse events are detailed in the Supplementary Material. All data were available as otherwise specified.

RESULTS

Case Series of LPV/RTV Associated With AKI in Patients With COVID-19

We observed 8 cases of patients treated with LPV/RTV who presented with AKI. They were all admitted for COVID-19, and 5 of 8 (62.5%) were men. They required intensive care with a median Sequential Organ Failure Assessment score of 7 (IQR, 5–10); moreover, 7 of 8 (87.5%) patients required vasopressor support agents. The median time to onset was 1 (range, 0–2) days. In these patients, proteinuria was observed in 6 of 8 patients (75%) and hematuria in 4 of 8 patients (50%). Two patients required dialysis (Table 1).

Analysis of Cases of AKI Associated With LPV/RTV in VigiBase

Among 22,035,564 individual case safety reports in VigiBase there were 162 cases of AKI associated with LPV/RTV reported from 55 countries. The information component of the association of LPV/RTV with AKI was significant (IC = 1.5; IC_{025} = 1.3). The first case was reported in 2001 and IC became significant in 2003. This year (2020) saw the highest number of events reported of the last 5-year period, with 13 cases (Figure 1). The median age was 50 years (range, 41–60 years). Men represented 109 of 162 (67.3%) cases and women 45 of 162 (27.8%) cases and the sex was unknown in 8 of 162 (4.9%) cases. The main indication was HIV in 152 of 162 (93.8%) patients and COVID-19 in 10 of 162 (6.2%) patients. The time to onset was longer in patients with HIV than in patients with COVID-19 (185 [range, 17–526] vs. 3 [range, 0–5] days; $P < 0.0001$). Overall mortality (associated or not) after these AKI events was 28 of 162 (17.2%) of patients, with no significant difference between patients with COVID-19 and patients with HIV (2/10 [20%] vs. 22/152 [14.5%], respectively; $P = 0.81$). LPV/RTV was the only incriminated drug in 23 of 162 (14.2%) cases (13/152 [8.6%] in HIV vs. 10/10 [100%] in patients with COVID-19; $P < 0.0001$; see Supplementary Figure S1 for detail on concurrently reported drugs). In patients with HIV, coreported renal adverse events were lactic acidosis (15/152 [10%]) and Fanconi syndrome (12/152 [8%]), with few cases of proteinuria (2.7%) and hematuria (2.7%). Associated renal adverse events were not reported in patients with COVID-19 in VigiBase.

DISCUSSION

Until 2020, LPV/RTV was mainly indicated in patients with HIV. Acute interstitial nephritis has been described in these patients. Drug-mediated acute interstitial nephritis is identified as a cause in a majority of cases after extended use and often presents as proximal tubular injury.[6] In patients with HIV, drugs commonly associated with acute interstitial nephritis include nonsteroidal anti-inflammatory drugs, sulfamethoxazole/trimethoprim, and antiretroviral therapy. Antiretroviral-related nephrotoxicity is mainly caused by tenofovir with Fanconi syndrome. Moreover, it is often associated with low-dose RTV, decreasing the renal clearance of tenofovir. In VigiBase, Fanconi syndrome was described in 12% of AKI events in patients with HIV, which may be related to cotreatment with other antiretroviral therapy in 90% of patients (mostly tenofovir and emtricitabine). Lactic acidosis was coreported in 10%, partly because of mitochondrial cytopathy, like those taking stavudine and didanosine.

During the COVID-19 pandemic, AKI incidence ranged from 5%–29% depending on patients' severity with coreported proteinuria and hematuria.[7] The virus targets angiotensin-converting enzyme II. This enzyme is expressed in the lungs but has been reported in the kidney, confirmed on postmortem biopsy specimens with viral inclusion in tubular epithelial cells and podocytes. Tubular damage through direct cytotoxicity or by immune-mediated tubule pathogenesis may be involved in COVID-19–related AKI.[8]

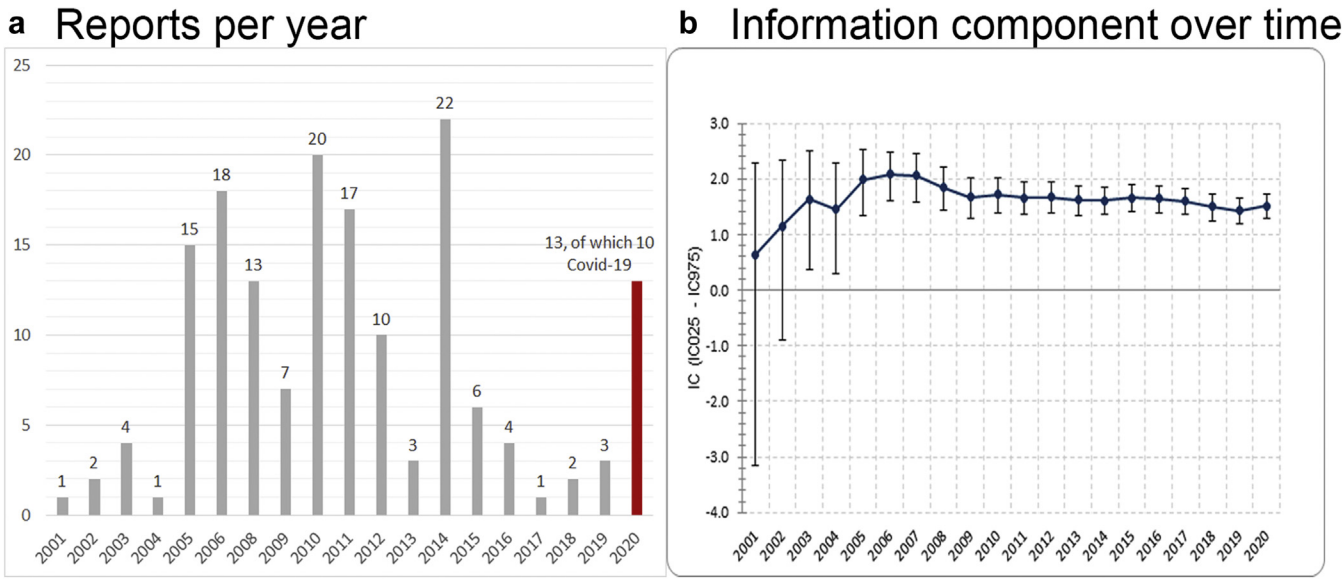

Figure 1. Evolution of (a) reporting and (b) information component (IC) of lopinavir/ritonavir-associated acute kidney injury in the World Health Organization pharmacovigilance database VigiBase, as of May 2020. COVID-19, coronavirus disease 2019.

These elements may explain the differences we observed when comparing LPV/RTV-associated AKI in HIV and COVID-19. In our case series patients were severe, with high admission Sequential Organ Failure Assessment scores, and most needed vasopressor support. Moreover, the time to onset was much shorter than that of previously described AKI in patients with HIV, which points toward the role of sepsis related to COVID-19, which may be, in this case, a major confounding element. Aggravating factors such as low perfusion caused by vasoconstrictive agents, hypoxia, rhabdomyolysis, inflammation related to cytokine release syndrome, and immune-mediated tubulopathy with $CD68^{+}$ macrophage and C5b-9 deposition may be intertwined on top of the tubular damage observed in COVID-19.[9] After the observation that LPV/RTV did not benefit our patients and was associated with AKI we did not pursue this treatment in patients with COVID-19 who were admitted to our ward.

We acknowledge several limitations of this study, mostly underreporting associated with halo bias and lack of information. The likelihood of a causal relationship is not the same in all reports. Missing data are another limitation in pharmacovigilance database extractions. Analyzes were performed on overreporting and not the assessment of true relative risk, which would require the absolute number of exposed patients, which was missing in our study. It must be noted that disproportionality analysis allows us to focus the attention of clinical physicians and to assess plausibility of the incrimination of a drug toward a singular adverse event (i.e., LPV/RTV with AKI).

CONCLUSION

AKI associated with LPV/RTV was previously reported in the World Health Organization pharmacovigilance database for HIV indication, and COVID-19 saw a rise in these reports. COVID-19 may inherently cause AKI, and the possible synergistic effects of LPV/RTV and COVID-19 on AKI need to be further investigated.

DISCLOSURE

All the authors declared no competing interests.

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The supplied data from VigiBase come from various sources. The likelihood of a causal relationship is not the same in all reports. The information does not represent the opinion of the World Health Organization. The data, analytic methods, and study materials are available to other researchers for purposes of reproducing the results or replicating the procedure at http://www.vigiaccess.org/. In addition, the 8 cases described herein were reported in the French pharmacovigilance database (but were not implemented in VigiBase yet), and description of these drug-associated adverse events fall under relevant authorizations.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Material. Statistics related to information component (IC) computation, based on individual case safety report (ICSR) and adverse drugs reactions (ADR), and references for Information component analysis.

Table S1. Categorization of MedDRA Preferred Terms (PT level) regarding renal adverse events.

Figure S1. Overlap between LPV/RTV and other drugs incriminated in AKI in VigiBase.

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