PHARMACOVIGILANCE

Safety profile of the lopinavir/ritonavir combination before and during the SARS-CoV-2 pandemic

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Summary

Introduction. — When the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic began, there were no effective treatments assessed by clinical trials. In this context, in France, the French Public Health Council issued, from 5 March, 2020, several proposed recommendations for the therapeutic management of this new disease. This included the use of combination lopinavir/ritonavir, which is usually indicated as HIV treatment. Thanks to the reporting of adverse drug reactions (ADRs) to the French Regional Pharmacovigilance Centers, several safety signals including hepatobiliary and cardiovascular were quickly identified.
Objective. — This study aimed to compare the ADRs reported with lopinavir/ritonavir used in its usual indication prior to the pandemic with the ADRs reported with the coronavirus disease 2019 (COVID-19) indication.

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Methods. — Cases of ADRs were extracted from the French Pharmacovigilance Database. ADRs were compared between the two periods: pre-COVID (1985 to 31 December 2019) and COVID (1 January 2020 to 21 July 2020).

Results. — Patients with COVID-19 were found to have a different safety profile, with significantly more damage to the liver (43% of ADRs), heart (10.6%) and kidneys (7.1%). The ADRs reported before the pandemic were mainly gastrointestinal and cutaneous.

Conclusions. — This different safety profile may be related to the effect of the virus on the organs, the patient profile (age, medical history...) and the drugs associated with lopinavir/ritonavir. Our study should serve as a reminder that the safety profile of a drug can depend on its use. Spontaneous reporting and pharmacovigilance have a critical role in alerting health professionals to ''new'' ADRs reported with well-known drugs.

Introduction

When the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic began, in March 2020, there were no effective treatments assessed by clinical trials. In France, several drugs were used to manage this emergent disease in the early period, following recommendations proposed by the French Public Health Council [1], including:

- remdesivir, an antiviral drug developed for the treatment of Ebola-related diseases and for which data were available for other coronaviruses (SARS-CoV and Middle East respiratory syndrome coronavirus [MERS-CoV]). As early as February 2020, specific pharmacodynamic data on SARS-CoV-2 were available;
- chloroquine, and secondarily hydroxychloroquine, in view of in vitro antiviral action with data available for SARS-CoV and MERS-CoV;
- immunomodulators such as anti-Il6 (tocilizumab in particular) in connection with their potentially beneficial action in the treatment of cytokine release syndromes;
- combination of lopinavir-ritonavir (LOPI/RITO), used since the early 2000s in the treatment of HIV and for which data have been available for other coronaviruses (SARS-CoV and MERS-CoV). Based on the available data, the recommended dose of LOPI/RITO was the same as that for the treatment of human deficiency virus (HIV) infection in adults: LOPI/RITO 200/50 mg 2 tablets twice daily for 10—14 days [2].

In June 2020, the most commonly used drugs in France, outside of marketing authorization and clinical trials, were hydroxychloroquine and LOPI/RITO [3]. However, on 15 July, 2020, the French Public Health Council advised against their use on the basis of available data which did not provide sufficient evidence of their effectiveness in treating COVID-19 [4].

In this particular context, the French pharmacovigilance network was very attentive to the use of these drugs. On 26 March, 2020, two serious cases of cardiovascular complications following the administration of hydroxychloroquine were notified by health care professionals and were reported by the French Regional Pharmacovigilance Centers (RPVC) to the French National Agency for the Safety of Medicines and Health Products (Agence nationale de sécurité du médicament et des produits de santé [ANSM]). A national pharmacovigilance survey was set up on 27 March [5]. The objective of this survey was to ensure the continuous monitoring of adverse drug reactions (ADRs) to all drugs used in patients with COVID-19 apart from clinical trials. The scope of the survey was not only ADRs for drugs used outside their marketing authorization, but also, more broadly, ADRs for all drugs administered to these patients. In addition, the investigation aimed to detect drugs that could be suspected of promoting the infection or causing a more serious form of the disease than expected. The data were initially analyzed on a daily basis and discussed on a weekly basis within a specific committee at ANSM. A cardiovascular risk emerged with LOPI/RITO, along with renal and hepatic toxicities that appeared to be of concern due to their severity [3].

The aim of our study was to compare retrospectively all the ADRs reported with this drug used in its usual indication (HIV-1 infection), collected before the pandemic period, with those reported for COVID-19 in order to better describe the safety profile of this treatment.

Methods

Data source

We conducted a retrospective observational study. As detailed in a previous similar work for hydroxychloroquine [6], data were extracted from the French Pharmacovigilance Database from 1 January 1985 to 21 July 2020. The relationship between an ADR and a drug was assessed according to the French pharmacovigilance causality assessment method, which is based on chronology (from doubtful C1 to likely C3), semiology (from doubtful S0 to likely S3), and bibliography (from effect never published B0 to well-known

effect B3) [7,8]. The seriousness of each case was recorded according to the regulatory definition (European Medicines Agency — ICH Topic E 2 A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, June 1995, Guideline no. CPMP/ICH/377/95.). All ADRs are coded according to MedDRA (The Medical Dictionary for Regulatory Activities).

Study design and cases selection

All cases where LOPI/RITO was coded as ''suspect'' or ''interaction'' were included. Cases were split into 2 periods defined as ''pre-COVID'', from 1 January 1985 to 31 December 2019, and ''COVID'', corresponding to cases registered from 1 January 2020 to 21 July 2020 and concerning patients treated for COVID-19. These cases were identified by the coded indication and by reading the narrative of each case.

When possible, some ADRs initially classified into MedDRA system organ class (SOC) ''general disorders'', ''investigations'', ''lesions/intoxications'' or ''metabolic disorders'' were reclassified to a more appropriate SOC. This concerns preferred term (PT) clearly linked to on organ (e.g. ''transaminases increased'' in the SOC ''investigations'' reclassified into ''hepatobiliary disorders''). These modified SOC are identified in this study as ''modified system organ classes'' (SOC_m). The analysis was performed according to these SOC_m.

Data analysis

Quantitative variables were presented as means and standard deviations (SD), median, minimum and maximum values or frequencies with percentages (%). Qualitative variables were assessed by Chi^2 or Fisher tests, and quantitative variables by a Z-test of reduced deviation. The chosen risk of error was 5%. A P-value of < 0.05 was considered statically significant. All analyses were conducted using Microsoft Office Excel® 2010 (Microsoft, USA) and biostaTGV [9].

Results

Baseline characteristics

In the pre-COVID period, a total of 1629 cases were included. LOPI/RITO as the only suspected drug in 433 (27%). Indication was HIV in all cases. Main characteristics are detailed in Table 1. Of these cases, 3.5% involve exposure during pregnancy and 3.8% were resulting from a drug-drug interaction. These 1629 cases were reported over a 19-year period, averaging 81 cases per year, with more cases reported between 2001 and 2008, shortly after the drug was marketed, and a clear decrease after 2010.

During the COVID period, a total of 192 cases were included over a 7-month period. LOPI/RITO was the only suspected drug in 62 (32%) cases. LOPI/RITO was used for the treatment of COVID in all cases. There were 32.3% of the cases associated with an overdose (plasma concentrations over the usual therapeutic range) and 5.2% resulting from drug-drug interactions.

The population was mainly male (about 2/3 of patients) for both periods. However, there was a significantly higher proportion of males in the pre-COVID population, and the population was significantly older in the COVID period ($P < 0.05$).

Reports overwhelmingly originated from hospital healthcare professionals in both cases (96% vs. 98%) with a majority of specialist physicians reporting in the pre-COVID period (92%) and a split between hospital pharmacists (54%) and specialist physicians (44%) in the COVID period.

Seriousness and outcome

Compared to the pre-COVID period, the proportion of serious cases was significantly higher during the COVID period ($P < 0.01$), but serious cases were mainly ''hospitalization'' in pre-COVID period and ''other serious'' in COVID period.

The outcome of ADRs was favorable (recovery or recovery in progress) in 54% of cases during the pre-COVID period and 78% of cases during the COVID period.

During the pre-COVID period, 31 deaths (1.9% of cases) were attributed to LOPI/RITO in association with other suspected drugs, except in 2 cases. The fatal outcomes were found to be of varying origins.

During the COVID period, 4 deaths (2.1% of cases) were attributed to LOPI/RITO, although it was not the only suspected drug in these cases. Again, the fatal outcomes were found to be of varying origins.

Causality of LOPI/RITO

The chronological criterion was higher in the COVID period, with plausible chronology (C2) in 57% and suggestive chronology (C3) in 6.3% of cases versus respectively 37% and 3% in pre-COVID cases. Doubtful chronology (C1) was mainly found in the pre-COVID period (59% vs. 35% in COVID period).

The semiological criterion was proportionally comparable for the 2 periods and was mostly doubtful semiology (S1): 75% in the pre-COVID period and 50% in the COVID period.

For both periods, the most reported bibliographic criterion was B3 (expected), i.e. the majority of ADRs were found in the French Summary of Product Characteristics (SPC) of LOPI/RITO (KALETRA®) [3]: 70% in the pre-COVID period and 88% in the COVID period.

Comparison of ADR classified by SOCm

SOCm classes whose incidence during at least one of the 2 periods was greater than 2% were compared statistically (Table 2).

Compared to the pre-COVID period, hepatobiliary disorders were significantly more frequent in the COVID period, accounting for 42% of the events (vs. 6.7%), as were cardiac and renal disorders.

The 10 most frequent PT in pre-COVID period were: ''diarrhea'' (14.9%), ''lipodystrophy acquired'' (5.0%), ''nausea'' (2.4%), ''vomiting'' (2.9%), ''hypertriglyceridemia'' (3.3%), ''dyslipidemia'' (1.9%), ''rash'' (1.8%), ''abdominal pain'' and ''hypercholesterolemia'' (1.6% each), ''pruritus'' (1.4%) and ''acute kidney injury'' (1.3%).

The 10 most frequent PT in COVID period were: ''hepatocellular injury'' (17.8%), ''diarrhea'' (9.6%),

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Table 1 Baseline characteristics.

	Pre-COVID (2000—Dec 2019)	COVID (Jan—July 2020)
Number of case reports	1629	192
Number of ADRs	2553	322
Gender[a,b]		
Ratio men/women	0.71	0.64
Age (years)[a,c]		
Mean (± SD)	42.4 (± 11.3)	63.5 (± 24.2)
Median	42	65
Min—Max	0.022—82	20—92
'Pregnancy' reports		
n (%)	56	0
'Drug interaction' reports		
n (%)	62	10
Serious cases (%)	571 (35%)	114 (59%)
Seriousness criteria (WHO criteria)		
Death	31 (5.4%)	4 (3.5%)
Life-threatening	51 (8.9%)	6 (5.3%)
Incapacity/disability	22 (3.9%)	0
Birth defect	7 (1.2%)	0
Hospitalization	393 (68.8%)	39 (34.2%)
Other	67 (11.7%)	65 (57%)

ADRs: adverse drug reactions; COVID: coronavirus disease; WHO: World Health Organization.
[a] Infants of pregnant cases were not included in the gender and age analysis.
[b] Patient gender unknown for 10 patients of the pre-COVID period.
[c] Patient age unknown for 18 patients of the pre-COVID period.

Table 2 Comparison of frequency of events between the 2 periods for lopinavir/ritonavir cases (incidence > 2%).

SOC$_m$	Number of ADRs (%) pre-COVID	Number of ADRs (%) COVID
Gastrointestinal disorders*	**661 (25.9%)**	49 (15.2%)
Cutaneous disorders*	**357 (14.0%)**	2 (0.6%)
Metabolic disorders*	**281 (11.0%)**	15 (4.7%)
Hepatobiliary disorders*	170 (6.7%)	**138 (42.9%)**
Neurological disorders*	149 (5.8%)	4 (1.2%)
General disorders*	144 (5.6%)	8 (2.5%)
Haematological disorders*	123 (4.8%)	2 (0.6%)
Musculoskeletal disorders	101 (4.3%)	6 (1.9%)
Renal disorders*	97 (3.6%)	23 (7.1%)
Cardiac disorders*	71 (2.8%)	**34 (10.6%)**
Psychiatric disorders	53 (2.1%)	2 (0.6%)
Investigations	52 (2.0%)	25 (7.8%)
Lesions*	11 (0.4%)	9 (2.8%)
Others	283 (11%)	5 (1.6%)

ADRs: adverse drug reactions; COVID: coronavirus disease; SOC: system organ class. Data in bold are the 3 most frequent SOCm.
* $P < 0.05$.

''drug level increased''/''Antiviral drug level above therapeutic'' (7.4%), ''electrocardiogram QT prolonged'' (5.6%), ''acute kidney injury'' (5.3%), ''cholestasis'' and ''hyperbilirubinemia'' (4.3% each), ''hypertriglyceridemia'' (3.7%), ''hypertransaminemia'' (3.1%) and ''nausea'' (2.5%).

Drug interactions

In the pre-COVID period, 62 cases of drug interactions were identified. These cases involved 35 different molecules. The most involved drug classes were anti-vitamin K (11 cases), inhaled corticosteroids (11 cases), anti-cancer drugs

(9 cases), levothroxine (8 cases), ergot derivatives (5 cases), anti-epileptics, antituberculosis and antihypertensive drugs (4 cases each). All cases were consecutive of a pharmacokinetic interaction.

In the COVID-period, 10 cases were identified, involving 10 different molecules. The most involved drugs were immunosuppressive in 4 cases (tacrolimus/everolimus), atorvastatine in 2 cases, azithromycine in 2 cases. Cases were mainly consecutive of a pharmacokinetic interaction except 4 cases resulting from a pharmacodynamic interactions. ADR in interacting cases were cardiac ($n = 7$), increase in drug concentrations ($n = 3$), renal failure ($n = 3$), rhabdomyolysis ($n = 2$), digestive ($n = 2$), neurologic ($n = 2$).

Discussion

Our study found that the most frequently reported ADRs were significantly different between pre-COVID period and COVID-period. The most significant differences were observed for hepatobiliary, cardiac and renal disorders. Cardiac and hepatobiliary were also identified in the COVID-period for hydroxychloroquine [6].

Hepatobiliary disorders, which represented 7% of the disorders in the pre-COVID period, increased to 43% in the COVID period. In COVID-19 cases, the pattern of liver damage was predominantly hepatocellular, with only three severe cases associating hepatic cytolysis, hyperbilirubinemia and decrease of prothrombin time. The outcome of these cases was rapidly favorable after withdrawal of LOPI/RITO. COVID itself may be involved in liver injury, and several case reports have described severe liver function abnormalities or severe or chronic liver failure in patients diagnosed with COVID-19 [10]. Several reasons have been proposed to explain the hepatic lesions seen in patients with COVID-19 [11]. This includes direct infection of hepatocytes and/or cholangiocytes with the virus, micro-thrombotic complications, immune dysregulation, drugs toxicity, hypoxia-related hepatic ischemia and multi-organ failure. All could play a role in the occurrence of liver toxicity under LOPI/RITO. The LOPI/RITO combination itself has been found in several studies to be particularly associated with hepatic injury in COVID-19, including a disproportionality analysis of US Food and Drug Administration pharmacovigilance database [12,13].

Cardiac disorders under LOPI/RITO were also more frequent in the COVID period (11% versus 3%), and QT prolongation was the 4th most reported ADR. Cardiac disorders under LOPI/RITO have already been the subject of publications by Fresse et al. (2020), who used the same database as us [14]. Several possible reasons for the increased risk of cardiac toxicity have been suggested by Funck-Brentano et al. [15]. First, the increased incidence could be related to the impact of SARS-CoV2 on the heart. Indeed, coronavirus-infected patients have multiple risk factors for drug-induced rhythm disorders: frequent hypokalemia, fever (which amplifies drug-induced cardiac channel blockade), and the increased IL-6 concentrations observed in the infection, which could be a mechanism of QT prolongation associated with inflammation. According to Guo et al., about 30% of patients hospitalized with COVID-19 in a Chinese hospital had myocardial injury associated

with cardiac dysfunction and arrhythmias. These myocardial lesions were significantly associated with fatal outcomes [16]. Also, many patients received other QT prolongation-inducing drugs in combination with LOPI/RITO. In our work, there were several cases of potential drug interactions due to the combined effects of LOPI/RITO and azithromycin, ciprofloxacin, amiodarone, and flecainide in particular.

Another significant difference between the two periods was the occurrence of acute renal failure, which was listed as the most frequent PT (5th ADR) in the COVID period. In July 2020, the independent committee of the Discovery clinical trial, which thoroughly analyzed adverse events in treated patients, highlighted the significantly higher frequency of serious adverse events concerning renal function in both groups of patients receiving LOPI/RITO, particularly in patients hospitalized in intensive care [17]. It should be noted that previous studies have shown an increased risk of acute kidney injury in hospitalized patients infected with SARS-CoV-2 [18]. A potential explanation for this observation was provided by Braun et al., whose post-mortem study found that the virus has a renal tropism: the RNA of the virus was found in the kidneys of 60% of patients [19]. In our study, in most of cases, other drugs were suspected especially antibiotics. A drug interaction leading to renal failure was found in 3 cases (tacrolimus in 2 and apixaban in 1).

The difference in safety profile may also be related to the difference between the populations. The patients receiving LOPI/RITO in the pre-COVID period were all treated for HIV. The population was 71% male with a median age of 42 years and treated for HIV. This is in agreement with the French National Authority for Health (Haute Autorité de santé [HAS]) data describing the characteristics of patients treated with LOPI/RITO in 2009, where 72.4% of patients were male and the median age was 39.1 years [20]. Regarding the population in the COVID period, the included cases had a median age of 65 years (all adults), and were predominantly male (64%), similar to the study conducted with hydroxychloroquine [6]. COVID patients were significantly older than in the pre-COVID population as described by Santé Publique France in May 2020 [21]. The most severely affected patients with COVID-19 were over 60 years of age, 54% of patients in intensive care were over 65 years of age, severe forms were exceptional in children, and more males (about 70%) than females were admitted to intensive care. In its weekly report of May 17, 2020, the WHO reported that severe forms of the disease were most common in men over 60 years of age with chronic diseases (hypertension, heart failure, diabetes) and that 60% of deaths occurred in men [22]. The comorbidities and risk factors for some ADRs are therefore different between the patients of these 2 periods. As shown by Lee, the incidence of ADR used in COVID-19 management was higher in patients with one or more comorbidities [23]. Moreover, taking into account these comorbidities and the disease treated, the concomitant drugs are also different (especially antibiotics, cardiovascular and immunosuppressive drugs in COVID-19 patients). We found a drug interaction in 5.2% of cases in COVID-19 patients (versus 3.8% in pre-COVID period). As many antiviral drugs, the risk of drug interaction with LOPI/RITO should be considered before prescribing [24].

Of note, 32.3% of the cases included in our study were associated with lopinavir overdose. ADR were mainly

hepatic (45%) and digestive (20%) in these cases. Two French studies reported extremely higher plasma concentrations of LOPI/RITO in COVID-19 patients than in HIV-infected patients, of about five times more (18,000 ng/mL versus 5365 ng/mL with 400 mg/12 h) [25,26]. Lopinavir is metabolized by cytochrome P450 3A4 isoenzyme and it is well-known that infection and inflammation are associated with down-regulation of cytochrome P450. Hence, in patients with COVID associated with a high inflammatory pattern, this could have led to a reduce LOPI/RITO metabolism resulting a very high plasma exposure in the majority of patients. About one over five patients prematurely withdrew LOPI/RITO because of moderate ADRs (hepatic or gastrointestinal). Clinicians should only lower dosage based on clinical and biological safety criteria rather than only on plasma concentrations.

Our study has some limitations. Not all adverse events are reported to RPVC. Indeed, pharmacovigilance is not intended to collect all adverse drug reactions, unlike clinical trials. The rate of under-reporting is estimated at 90% according to the study by Hazell et al. [27]. But this new indication in the context of the pandemic has probably limited this bias. There is also a notoriety bias, which is to say that once the risk is known the rate of reporting may be increased. This could be observed in the COVID period considering the communications made.

The strength of this study is that it compares data from the same collection and analysis methodology over a 35-year period [28]. The cases are all analyzed and medically assessed by pharmacovigilance experts before registration into the database.

Conclusion

Our study clearly highlights different adverse event profiles for LOPI/RITO in COVID-19 patients. Hepatobiliary, cardiac and renal adverse events on LOPI/RITO were more frequently reported during the COVID period than in the pre-COVID period, where the most frequent events were gastrointestinal, dermatological and metabolic. These inconsistencies may be attributed to several aspects, including the SARS-CoV-2 infection itself, which affects not only the respiratory tract but also other organs, the effect of co-medication, and the patients itself (age, comorbidities).

This study highlights the role of the French Pharmacovigilance Network to identify a particular safety profile of a drug used off label, even for old an experienced drug such as LOPI/RITO and then have a critical role to play in warning healthcare professionals of these evolving safety profiles.

Authors' contribution

All authors have contributed to the work: Pauline Lory and Aurélie Grandvuillemin conducted the study and wrote the manuscript; Sandrine Combret, Joelle Michot, Gwenaelle Veyrac and Laurent Chouchana reviewed the manuscript.

All of them are aware of this submission and agreed about it.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Disclosure of interest

The authors declare that they have no competing interest.

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