Prescribing practices of lopinavir/ritonavir, hydroxychloroquine and azithromycin during the COVID-19 epidemic crisis and pharmaceutical interventions in a French teaching hospital

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ABSTRACT
Objective The aims of this study were to describe prescribing practices of lopinavir/ritonavir, hydroxychloroquine and azithromycin during the COVID-19 epidemic crisis (primary endpoint), then to characterise pharmaceutical interventions (PIs) targeted to these medications and evaluate the impact of these PIs on prescribers’ practices (secondary end-points).

Methods This retrospective observational study was carried out at the University Hospital of Strasbourg (France) from March to April 2020. The analysed population excluded patients from intensive care units but included all other adult patients with COVID-19 who received at least one dose of lopinavir/ritonavir combination, hydroxychloroquine or azithromycin, while inpatients. Analyses were performed by using data extracted from electronic medical records.

Result During the study period, 278 patients were included. A rapid decrease in lopinavir/ritonavir prescriptions was observed. This was accompanied by an increase in hydroxychloroquine and azithromycin prescriptions until the end of March, followed by a decrease leading to the disappearance of these two medications in April. The pharmaceutical analysis of the prescriptions resulted in 59 PIs of which 21 were associated with lopinavir/ritonavir, 32 with hydroxychloroquine and 6 with azithromycin. Regarding the medication-related problems, the most frequent ones were incorrect treatment durations (n=32 (54.2%)), drug interactions with potential torsadogenic reactions (n=14 (23.7%)) and incorrect dosing (n=16 (10.2%)). From the 59 PIs, 48 (81.4%) were accepted and physicians adjusted the medication regimens in a timely manner.

Conclusion This study demonstrated the value—even more meaningful in a crisis situation—of a strong synergy between physicians and pharmacists for patients’ safety focused practices.

INTRODUCTION
The health crisis linked to the epidemic of Coronavirus Disease 2019 (COVID-19) caused by the new coronavirus (SARS-CoV-2) strongly mobilised healthcare institutions. This led hospitals to strengthen their organisation with the main objectives of admitting COVID-19 patients without restriction and providing optimal and safe care.1

The University Hospital of Strasbourg (UHS) was one of the first in France to be affected by SARS-CoV-2 and responded quickly to the extremely rapid kinetics of patients’ admission.2 Pharmacists implemented various strategies to provide pharmaceutical care, including close monitoring of medication for all the hospitalised COVID-19 patients.

No specific medication was confirmed to treat COVID-19 during the epidemic crisis.3 4 The safety and efficacy of medications proposed by clinicians as part of research protocols or routine care were uncertain, and some such as lopinavir/ritonavir combination, hydroxychloroquine and azithromycin could cause serious adverse reactions.5–7 Therefore, it was important for hospital pharmacists to be actively involved in evidence-based decision making regarding such medications and to assist clinicians in formulating and adjusting medication regimens in a timely manner.

The objectives of this study were first to describe prescribing practices of lopinavir/ritonavir combination, hydroxychloroquine and azithromycin during the epidemic crisis, second to characterise the pharmaceutical interventions (PIs) targeted to these medications, and third to evaluate the impact of PIs on prescribers’ practices.

METHOD
Study design This was a single-centre retrospective observational study conducted at UHS between 17 March and 19 April 2020. UHS is a public teaching hospital and the largest hospital in the eastern part of France, with a total of 2600 beds. The clinical department heads gave their consent to access the patients’ medical records. Moreover, the hospital booklet states that “in order to enhance the management and the safety of the patients, the hospital can use data from medical records on the condition that the access remains confidential and anonymous”. Information strictly required for the purpose of the study was thus collected in an anonymised manner.

Inclusion and exclusion criteria The included patients were hospitalised patients in conventional units with COVID-19 (positive SARS-CoV-2 reverse-transcription PCR or chest CT
with typical imaging of COVID-19) and who received at least one dose of lopinavir/ritonavir combination, hydroxychloroquine or azithromycin.

The population analysed excluded patients from intensive care units.

Data collection
PIs were routinely recorded in DxCare patients’ electronic medical records. For the purpose of the study, data (ie, demographic data, medications, comorbidities and PIs) were extracted from DxCare using BO application (Business Object – SAP France). The outcome of each PI was retrospectively searched in patient records and classified as “implemented”, “not implemented” or “unknown”.

Pharmaceutical intervention
Pharmaceutical analyses were structured and carried out according to a systematic and standard method including: search for potential medication redundancies, availability of medications, pathophysiological contraindications, dosages, durations, modalities and rhythms of administration, and drug interactions. The online tools used by pharmacists were: Summary of product characteristics (http://agence-prd.ansm.sante.fr/php/ecdex/index.php), the French national thesaurus of interactions (https://ansm.sante.fr/Dossiers/Interactions-medicamentueuses/Interactions-medicamenteuses/(offset)/0), the COVID-19 drug interactions website from the University of Liverpool (https://www.covid19-druginteractions.org/checker), crediblemeds (https://www.crediblemeds.org/) and that of the reference centre on teratogenic agents (CRAT, https://www.lecrat.fr/).

Lopinavir/ritonavir combination, hydroxychloroquine and azithromycin were prescribed off label. To assist clinicians in better understanding and prescribing these medications, an expert group of clinical pharmacists, infectiologists, virologists and hygienists reviewed the existing literature and French consensus (on a regular basis during the study period). This group created a rational use guideline, updated several times, including duration of treatments, contraindications, monitoring, interactions and adjustment for special populations, such as pregnant women populations (for details, please see online supplemental material). Based on this guideline which followed the evolution of the French national recommendations, pharmacists and pharmacy residents formulated PIs (ie, recommendations in response to medication-related problems (MRPs)) after fully balancing clinical benefits and risks. The MRPs were encoded according to the classification of the French Society of Clinical Pharmacy.9 The impact of PIs on prescribing was measured by their acceptence. Acceptance of a PI corresponded to the implementation of the pharmaceutical recommendations by the clinicians. The COVID-19 prescriptions were daily analysed and validated.

A total of seven pharmacists and eight pharmacy residents participated in the analysis of weekday prescriptions for patients with COVID-19. At night and on weekends, pharmacy residents were on site to respond to urgent needs. In case of disagreement between pharmacists and physicians, details of the clinical situations were forwarded to the expert group to resolve discrepancies.

Data analysis
Patient characteristics and study results were expressed using proportions, means with SD.

RESULTS
Lopinavir/ritonavir combination, hydroxychloroquine and azithromycin prescriptions
During the study period, 1449 COVID-19 patients were hospitalised, 1193 of whom were admitted to standard care units. Of these 1193 patients, 278 were treated with at least one of the three medications: lopinavir/ritonavir combination, hydroxychloroquine and azithromycin. The mean (SD) age of the patients was 59.9±14.8 years and the male-to-female ratio was 1.5.

Six hundred and eighty-six prescriptions corresponding to the 278 patients were completed. Pharmacists analysed and validated 483 of them (70.4%). Two hundred and three prescriptions did not benefit from pharmaceutical analysis and validation. Of these, 180 were of very short duration (prescription duration <1 day): 3, 68 and 109 for lopinavir/ritonavir combination, hydroxychloroquine and azithromycin, respectively. For the remaining 23 prescriptions, 15 patients went home and eight were transferred to intensive care units.

Figure 1 illustrates the kinetic of the prescribing practices of lopinavir/ritonavir combination, hydroxychloroquine and azithromycin at the UHS during the study period.

Pharmaceutical interventions
Fifty-nine PIs (12.2% of the analysed prescriptions) were performed for 53 patients (19.1%). The mean age of these patients was 58.0±14.6 years and the male-to-female ratio was 1.9. The numbers of patients, prescriptions and PIs are presented in table 1.

Regarding the MRPs, the most frequent ones were incorrect treatment durations (n=32 (54.2%)), torsadogenic drug interactions (n=14 (23.7%)) and incorrect dosing (n=6 (10.2%)), respectively. With regard to the 14 torsadogenic drug interactions, the following measures were taken: implementation of electrocardiographic (ECG) monitoring in seven cases, discontinuation of medication in six cases and change of medication in one case. No non-torsadogenic drug interaction was detected during the study period.

From the 59 PIs, 48 (81.4%) were accepted. In five cases (8.5%), the outcome of the proposed interventions was unknown, while in six cases the PIs were not implemented (four PIs were rejected by the physicians and in two cases the patients were transferred). The details of MRPs and PIs are presented in table 2. In addition, table 3 provides concrete examples.
The use of hydroxychloroquine exposes patients to numerous adverse reactions such as fulminant hepatic insufficiency, severe skin reactions and ventricular arrhythmia.6 11 12 These effects increase with prolonged use at high dosage. Special care is therefore essential in patients, in particular for those with congenital or acquired QT prolongation and/or with risk factors (heart disease, bradycardia, hypokalaemia, hypomagnesaemia, etc).13 Concerning azithromycin, it is also essential to avoid other medications at risk of QT prolongation, risk which is also increased in cases of hypokalaemia, hypomagnesaemia or bradycardia.14 The widespread publicity of small uncontrolled studies, which suggested that the combination of hydroxychloroquine with azithromycin was successful in clearing viral replication, led to a significant proportion of patients (n=77 patients) with the two medications in our hospital.15 16 Obviously, it exposed them to an enhanced risk of QT prolongation and adverse events.10

From the beginning of April, there was a significant reduction in the number of prescriptions of hydroxychloroquine and azithromycin. This cautious attitude towards the two medications anticipated the latest publications which showed not only an absence of therapeutic benefit but also a potential harm with the use of hydroxychloroquine (with or without azithromycin) in hospitalised patients with COVID-19. In this regard, a multinational analysis registry, including 96 032 patients published in the Lancet, showed a decrease in inpatient COVID-19 survival and an increase in ventricular arrhythmias. However, the methodology of this publication appeared controversial and the Lancet issued an "Expression of concern" to alert readers and finally withdrew the publication.17 However, other studies in the meantime concluded that hydroxychloroquine had no beneficial effects in patients with COVID-19.18 The National Health Service (NHS) in the UK, for example, decided to stop enrolling participants to the hydroxychloroquine arm of the RECOVERY (Randomised Evaluation of COVID-19 thErapY) trial after releasing preliminary results concerning a total of 1542 hospitalised patients.19

The most common MRPs in this study were duration of treatment, drug interactions and inappropriate dosing. These data differ from the literature, which usually primarily reports suboptimal dosing, inappropriate administration modalities and non-compliance with guidelines.8 20 21 The main reason for these differences was the changing scientific attitude regarding therapeutic strategies, dosage and duration of treatment during the epidemic crisis. It should be noted that PIs related to torsadogenic drug interactions were remarkably represented (23.7%). Although the level of severity of the MRPs was not analysed in this study, it is certain that such medication interactions represented the highest clinical risk. The very high rate of physician acceptance of PIs (85.7% of cases) is indicative of this clinical risk.

The overall average acceptance rate of clinical pharmacists’ interventions was 81.4%. Regarding studies with a setting of clinical pharmacists, this rate of acceptance is in agreement with the literature.7 19 20 The main reason for this level of acceptance reflects in our opinion the accepted integration of clinical pharmacists into the medication management of patients. In addition to PIs, clinical pharmacists provided continuing education and advice for both clinicians and nurses during the epidemic crisis. Furthermore, they also gave continuous information about updated guidelines and medication supply availability.

Our study has strengths and limitations. Regarding the strengths, some COVID-19 studies described that clinical pharmacists analysed prescriptions and provided feedback to physicians about medication use-related problems,12 13 but none specifically investigated the impact of pharmaceutical analysis on prescribing practices for lopinavir/ritonavir, hydroxychloroquine and azithromycin. The PIs, performed during this period, were potentially safe for the patients. Pharmacists were thus able to demonstrate their expert role, especially in the management of drug interactions.

Concerning the limitations, we did not include patients treated in intensive care units (n=316 patients treated at least with
### Table 2  
Pharmaceutical interventions performed in COVID-19 patients treated with lopinavir/ritonavir combination, hydroxychloroquine or azithromycin and characterisation of the associated medication-related problems, University Hospital of Strasbourg, France

<table>
<thead>
<tr>
<th></th>
<th>Lopinavir/ritonavir</th>
<th>Hydroxychloroquine</th>
<th>Azithromycin</th>
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<tbody>
<tr>
<td></td>
<td>PIs* implemented</td>
<td>PIs* not implemented</td>
<td>Outcome unknown</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non-conforming treatment duration</td>
<td>17</td>
<td>2</td>
<td>19</td>
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<tr>
<td>Incorrect dosage</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Drug interaction with:</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Azithromycin</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Erythromycin</td>
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<td>Rovamycin</td>
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<td>Haloperidol</td>
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<td>Tiapride</td>
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<td>Cyamemazine</td>
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<td>Hydroxyzine</td>
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<tr>
<td>Non-optimal drug intake plan</td>
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<tr>
<td>Hydro-electrolytic disorders</td>
<td></td>
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<tr>
<td>Error related to computerisation</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total number of PIs</td>
<td>21</td>
<td>32</td>
<td>6</td>
</tr>
<tr>
<td>Outcome of interventions (% of acceptance)</td>
<td>90.5%</td>
<td>78.1%</td>
<td>66.7%</td>
</tr>
</tbody>
</table>

*PIs, pharmaceutical interventions.†No ECG carried out to assess the QT interval before the PIs were performed. ECG, electrocardiogram.
The safety and efficacy of medications proposed by clinicians for their contribution to conducting pharmaceutical analysis: Anne Dory, Anne Hurt, Dominique Paya, Guillaume Meyer, Hassène Djededoua, Anne Cécile Gérout, Dominique Levêque and also Amélie Rousseau for proofreading and linguistic review of the manuscript.

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None declared.

Patient consent for publication
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CONCLUSION
As the COVID-19 epidemic crisis became more severe, the management of patients’ medications led practitioners to use off-label therapies in their daily practice. To avoid MRPs, daily pharmaceutical validation of COVID-19 medications was decided upon. Although clinical pharmacists did not follow up the impact of their PIs on the evolution of the clinical condition of the patients, many of the interventions highlighted significant drug interactions, including those related to the combination of hydroxychloroquine with torsadogenic medications.

Key messages

What is already known on this subject
► No specific medication was confirmed to treat COVID-19 during the epidemic crisis.
► The safety and efficacy of medications proposed by clinicians as part of research protocols or routine care were uncertain.

What this study adds
► Pharmaceutical interventions highlighted significant drug interactions, including those related to the combination of hydroxychloroquine with torsadogenic medications.
► These interventions illustrate the value—even more meaningful in a crisis situation—of a strong synergy between pharmacists and patient-safety focused practices.

Recently, because of an unfavourable risk/benefit ratio regarding COVID-19 patients, the French authorities no longer allow hydroxychloroquine to be prescribed and dispensed outside the framework of marketing authorisations.23 This latest update demonstrates that our strategy of strengthening the monitoring of COVID-19 medications with high potential clinical impact was adapted to this unique crisis situation.


