Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Therapie 77 (2022) 301—307

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PHARMACOVIGILANCE

Comparative study of the adverse event profile of hydroxychloroquine before and during the Sars-CoV2 pandemic

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Received 2 August 2021; accepted 23 December 2021
Available online 28 December 2021

KEYWORDS
Hydroxychloroquine;
Pharmacovigilance;
Adverse drug reactions

Summary
Aims. — At the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, there were no clinically-tested medications for the effective treatment of coronavirus disease. In this context, on 5 March 2020, the French Public Health Council issued several recommendations for the therapeutic management of this new disease, including the use of hydroxychloroquine (HCQ). An unexpected cardiovascular safety signal was quickly identified as being more frequent than expected thanks to the reports of adverse drug reactions (ADRs) submitted to French regional pharmacovigilance centres (RPVC). The objective of this study was to compare all ADRs reported with HCQ used in its usual indication, collected before the pandemic period (1985 to 31 December, 2019) with those reported with the coronavirus disease 2019 (COVID-19) indication (1 January to 21 July, 2020).
Methods. — For this purpose, reports were extracted from the French pharmacovigilance database and analysed for these two periods.

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https://doi.org/10.1016/j.therap.2021.12.015

Results. — Our study showed a different safety profile in COVID-19 patients with more cardiac disorders (57% of ADRs versus 5% before the pandemic period), especially QT interval prolongation, resulting from an interaction with azithromycin in more than 20% of cases. Hepatobiliary disorders were also significantly more frequent.
Conclusions. — These observations could be associated with the effect of the virus itself on the various organs, the profile of the patients treated, and concomitant drug treatments.

Abbreviations

ADRs	adverse drug reactions
ANSM	French Health Agency
COVID-19	coronavirus disease 2019
CT	clinical trial
ECG	electrocardiogram
HCQ	hydroxychloroquine
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MA	marketing authorisation
MedDRA	Medical Dictionary for Regulatory Activities
MERS-CoV	Middle East respiratory syndrome coronavirus
MSSO	Maintenance and Support Services Organization
PT	preferred term
RPVC	French regional pharmacovigilance centres
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviations
SOC	system organ classes
SOC_m	modified organ classes
WHO	World Health Organization

Introduction

In January 2020, the World Health Organization (WHO) identified an emerging virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was responsible for pneumonia cases reported in China starting in late 2019, leading to the coronavirus disease 2019 (COVID-19) pandemic declared in March 2020 [1]. In France, several drugs were initially used to manage COVID-19 following recommendations of the French Public Health Council, including [2]:

- 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-CoV2 were available;
- combination of lopinavir-ritonavir, used since the early 2000s in the treatment of human immunodeficiency virus (HIV) and for which data were available for other coronaviruses (SARS-CoV and MERS-CoV);
- chloroquine and secondarily hydroxychloroquine (HCQ) in view of potential antiviral action with in vitro data available for SARS-CoV and MERS-CoV. In vitro data for SARS-CoV2 were available in February 2020 for chloroquine and in March 2020 for HCQ;
- immunomodulators such as anti-IL6 (tocilizumab in particular) because of their potentially beneficial action in the treatment of cytokine release syndromes.

In its usual indications (rheumatoid arthritis, lupus, polymorphous light eruption), according to marketing authorisation (MA), the recommended dosage is 200 mg to 600 mg per day (maximum dosage). However, many clinical trials, around the world, used a higher dosage. In Europe, the Discovery clinical trial tested a loading dose of 400 mg twice daily on day 1 followed by a daily dose of 400 mg once daily for 9 days [3]. In June 2020, the most commonly used drugs outside of their MA and clinical trials (CT) were HCQ and lopinavir/ritonavir [4]. On 26 May 2020, in France, the order authorizing the use of HCQ and the lopinavir/ritonavir combination in COVID-19, excluding clinical trials, was repealed. On 15 July 2020, the French Public Health Council recognized that the current available data from the literature provided no evidence that treatments with a presumed antiviral effect were beneficial in COVID-19.

Thanks to reports from healthcare professionals, on 26 March 2020 the French regional pharmacovigilance centres (RPVC) alerted the French Health Agency (ANSM) of the first two serious cases of cardiovascular complications with HCQ, whether associated with azithromycin or not. A national pharmacovigilance survey was officially launched on 27 March. The objective of this ongoing survey was to ensure the continuous monitoring of adverse drug reactions (ADRs) to drugs used in patients with COVID-19 (non-clinical trials), not only with drugs used in this indication (thus outside their MA) but also more broadly, of ADRs for all drugs administered to these patients or suspected of having promoted the infection. The data were initially analysed on a daily basis and weekly discussed in a specific ANSM committee bringing together representatives of the RPVC and ANSM in order to identify potential warning signs, to consider the measures to be taken, and to alert health professionals and patients if necessary. The elements discussed were not only

spontaneous notification data, but also data from clinical trials conducted in France, data from the French Centres for Evaluation and Information on Drug Dependence and Addictovigilance, the French Poison control and Toxicovigilance Centre, and any other relevant safety data (literature, European Medicines Agency, etc.) [5]. HCQ was thus identified as being associated with cardiovascular risk and liver damage in the COVID-19 indication [4]. These ADRs, although previously described with this drug, appeared to be occurring more frequently than expected. In this context, we decided to compare all the ADRs reported with this drug used in its usual indications (rheumatoid arthritis, lupus, polymorphous light eruption), before the pandemic period (before 31 December, 2019), and in the COVID-19 indication in order to better describe its safety profile.

Methods

Data source

Data were extracted from the French Pharmacovigilance Database (which includes all ADRs reported to and pharmacologically validated by the 31 French Regional Pharmacovigilance Centers) from 1 January 1985 to 21 July 2020. The relationship between an ADR and a drug is assessed according to the French pharmacovigilance causality assessment method, which is based on chronology (from C1, doubtful, to C3, likely), semiology (from doubtful S0 to likely S3) and bibliography. The seriousness of each case is 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): a case is considered serious when it results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect or other situations that may require intervention to prevent one of the other outcomes listed above. All ADRs are coded according to the Medical Dictionary for Regulatory Activities (MedDRA), developed under the auspices of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and maintained by Maintenance and Support Services Organization (MSSO). MedDRA contains five hierarchical grouping levels, ranging from a very general description to a very specific description. The largest description is ''system organ classes'' (SOCs), based on either etiology, manifestation site, or purpose.

Study design and cases selection

Cases were split into two periods defined as ''pre-COVID'', from 1 January 1985 to 31 December 2019 (all indications combined), and ''COVID'', from 1 January 2020 to 21 July 2020 and concerning patients treated in the COVID-19 indication.

Several ADRs coded according to a MedDRA dictionary preferred term (PT) for a specific organ and yet classified as ''general disorders'', ''investigations'', ''lesions/intoxications'' or ''metabolic disorders'' have been reclassified into organ classes deemed more clinically appropriate, called modified organ classes (SOC_m). These PT primarily concerned ADRs that may be related to the cardiac and hepatobiliary organ classes. The analysis was performed on these SOC_m.

Data analysis

Quantitative variables were presented as means, standard deviations (SD), medians, 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 and biostaTGV [6].

Results

Baseline characteristics

During the pre-COVID period, 1715 cases were reported, and HCQ was the only drug imputed for 985 (57.4%) of these cases (Table 1).

During the COVID period, 254 cases were reported, and HCQ was the only suspected drug for 69 (27%). HCQ was used for the treatment of COVID in all cases. No other indications were found. Among COVID cases, 24% of ADRs were the consequence of drug-drug interactions, whereas only 0.3% of ADRs were attributed to drug-drug interactions during the pre-COVID period.

The population was predominantly female (71%) in the pre-COVID period, while it was predominantly male (65%) in the COVID period. The proportion of males was significantly higher among COVID cases than pre-COVID cases ($P < 0.05$), and the population was significantly older during the COVID period ($P < 0.05$).

The proportion of serious cases was also significantly higher during the COVID period ($P < 0.05$).

In the pre-COVID period, 2727 ADRs were reported versus 351 during the COVID period. The majority of ADRs had a favourable outcome considering that 53.5% (pre-COVID) and 67.5% (COVID) of cases recovered without sequelae.

The notifications originated from hospitals in 99% of cases during the COVID period and in 73% of cases during the pre-COVID period. They were mainly submitted by medical specialists and pharmacists.

Death analysis

During the pre-COVID period, 22 deaths were reported (HCQ was the only suspected drug in 3). Among these cases, 10 were from exposure during pregnancy, 5 were overdoses and 7 were from various causes: pancytopenia, septic shock, cardiac damage (1 cardiorespiratory arrest, 1 global cardiac decompensation, 1 ventricular tachycardia, 1 hypertrophic cardiomyopathy).

During the COVID period, 7 deaths were reported, including 1 case where HCQ was the only suspected drug (azithromycin was associated in the other cases). All 7

Table 1 Baseline characteristics.

	Pre-COVID (1985—Dec 2019)	COVID (Jan—July 2020)
Number of case reports	1715	254
Number of ADRs	2727	351
Number of serious reports (%)	1020 (59.5%)	211 (83.1%)
Gender[a]		
Ratio men/women	0.29	0.65
Age (years)[a]		
Mean (± SD)	50.8 (± 18.4)	61.2 (± 15.1)
Median	51	64
Min—max	4—91	4—92
'Pregnancy' reports *n* (%)		
n (%)	44 (2.6%)	1 (0.4%)
'Drug-drug interaction' reports		
n (%)	6 (0.3%)	61 (24%)
Fatal outcome		
n (%)	22 (1.3%)	7 (2.8%)

ADRs: adverse drug reactions; COVID: coronavirus disease.
[a] Infants of pregnant cases were not included in the gender and age analysis.

patients died of cardiac causes, with 3 cases of QT prolongation on electrocardiogram, 1 cardiac decompensation due to heart failure, and 3 cardiac arrests.

Comparison of ADRs classified by SOC

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

For each period, one type of ADR emerged with a much higher frequency than the others; skin disorders for the pre-COVID period (32.5%) and cardiac disorders (56.7%) for the COVID period. The rate of cardiac effects increased by more than 50 points between the two periods. The proportions of hepatobiliary and gastrointestinal events were also more frequently reported in the COVID period while neurological and haematological disorders were higher in the pre-COVID period.

In the COVID period, more than one third (37.6%) of overall events were classified as QT prolongation.

Drug interaction analysis

There was a high proportion of ''interactions'' cases (25%) during the COVID period. Sixty-one cases, of which 59 serious (97%), were reported. The most reported drug interaction was with azithromycin (80% of cases); the two drugs were often combined in COVID treatment. The ADRs were mainly cardiac in nature (92%) and resulted from a potentiating or additive effect between the drugs. For 55 of the 61 cases (90%), the most common PT was ''prolongation of the QT interval on the electrocardiogram (ECG)''.

Discussion

Our study, which ran until 21 July 2020, included 1715 cases of ADRs related to the use of HCQ in the pre-COVID period and 254 cases during the COVID period. There were thus 18 times more ADRs during the COVID period based on annual number of cases. We find few cases where HCQ is the only suspected drug during the COVID period (1/3). This can be explained by the fact that patients treated for COVID infection are most often polymedicated. On the other hand, HCQ was the only suspected drug in most cases reported in the pre-COVID period (57%), notably because it is prescribed alone within the framework of its MA.

In the pre-COVID period, the population treated with HCQ under its MA (lupus, rheumatoid arthritis) in our study was 71% female with a median age of 51 years (mean = 50.8 years). A survey published in 2014 by Mathian et al. reports that lupus patients have an average age of approximately 50 years and are 88% female [7]. As for rheumatoid arthritis, it is most common between the ages of 40 and 60 and also has a female predominance (80% of cases) [8]. The reported cases are therefore consistent with the target population for this drug.

In the COVID period, 65% of the notified reports were male, with a median age of 64 years. Only four cases involved children, and patients were significantly older than in the pre-COVID period. These characteristics reflect the data published by *Santé Publique France* in May 2020 [9]. The most severely affected COVID patients were over 60 years of age, and 54% of patients in intensive care units were over 65 years of age (WHO). Severe forms were exceptional in children, and more men (about 70%) than women were admitted to intensive care [9,10]. The WHO reported in its weekly report for 17 May 2020 that severe forms of the disease occurred mostly in men over 60 years of age with chronic diseases (high blood pressure, heart failure, diabetes) and that 60% of the deaths due to COVID-19 were in men [10].

The percentage of serious cases was significantly higher during the COVID period (83.1% versus 59.5%), and we observed a higher proportion of deaths during the same

Table 2 Comparison of frequencies of events between the 2 periods (incidence >2%).

SOC_m	Number of ADRs (%) ''pre-COVID''	Number of ADRs (%) ''COVID''
Cutaneous disorders*	885 (32.5%)	22(6.3%)
Neurological disorders*	251 (9.2%)	7 (2%)
Haematological disorders*	236 (8.7%)	9 (2.6%)
Eye disorders*	211 (7.7%)	7 (2.0%)
Gastrointestinal disorders	183 (6.7%)	33 (9.4%)
General disorders*	136 (5.0%)	7 (2.0%)
Cardiac disorders*	128 (4.7%)	199 (56.7%)
Hepatobiliary disorders*	121 (4.4%)	37 (10.5%)
Musculoskeletal disorders*	101 (3.7%)	1 (0.3%)
Hearing disorders*	74 (2.7%)	1 (0.3%)
Infections	71 (2.6%)	4 (1.1%)
Psychiatric disorders	65 (2.4%)	3 (0.9%)
Metabolic disorders*	30 (1.1%)	10 (2.8%)
Others	235 (8.6%)	11 (3.1%)

ADR: adverse drug reactions; COVID: coronavirus disease; SOC: system organ class.
* $P < 0.05$.

period (2.8% versus 1.3%). The causes of death were mainly cardiac, reflecting the severity of cardiovascular disorders induced by HCQ in this context.

Overall, ADRs are expected, i.e. listed in the French summary of product characteristics for PLAQUENIL® [11]. However, the most frequently reported ADRs differed significantly by time period. The most significant variations were observed for hepatobiliary, cardiac and skin disorders.

Hepatobiliary disorders, which accounted for 4.4% of adverse reactions before the COVID period, increased to 10.5% during the COVID period. Several case reports have described severe liver function abnormalities or severe or chronic liver failure in patients affected by SARS-CoV2 [12]. There are several possible reasons for this increase in liver toxicity. Direct infection of hepatocytes and/or cholangiocytes by the virus, ''microthombotic endotheliali-tis'', immune dysregulation, drugs and drug combinations, hypoxia-related hepatic ischemia, and multi-organ failure could all play a role in the occurrence of liver toxicity under HCQ.

Cardiac damage was the ADR most often recorded during the COVID period (56.7%), whereas it represented only 4.7% of ADRs in the pre-COVID period. QT interval prolongation accounted for 2/3 of cardiac events during the COVID period, and 40% of cases were the result of a drug interaction. In April 2020, the Nice Regional Centre of Pharmacovigilance in charge of analysing all cardiac ADRs associated with ''off-label'' use of hydroxychloroquine, azithromycin and lopinavir-ritonavir in COVID-19, found that 86% of these were associated with the use of HCQ, with about half of which co-treated with azithromycine [13]. These ADRs have been described by Romani et al. (2020), who compared cardiac ADRs recorded in the French Pharmacovigilance Database before and during the COVID-19 pandemic (between 1985 and May 2020). In the pre-COVID period, cardiomyopathy and conduction disorders were most common, while in the COVID period, ventricular rhythm and repolarization disorders were most reported [14]. Roustit et al. (2020) reported that in the largest randomized trial, QT was prolonged in 11% to 20% of patients receiving a combination of hydroxychloroquine and azithromycin and this proportion reached 25% with the highest dose of hydroxychloroquine (1200 mg/day for 10 days) in another clinic trial [15]. According to an analysis of the World Health Organization (WHO) pharmacovigilance database (Vigibase®) performed by Nguyen et al., reports of potentially lethal acute cardiac proarrhythmogenic effects leading to ventricular arrhythmias have been described mainly with azithromycin but also with hydroxychloroquine. Hydroxychloroquine was also associated with potentially lethal heart failure when exposure was prolonged over several months [16]. Montastruc et al. (2020) also analysed the WHO pharmacovigilance database but before the COVID-19 pandemic. They showed a relative high percentage of cardiac ADRs (cardiomyopathy + arrhythmias = 8.3% of total ADRs) [17]. Van den Broek et al. showed that HCQ-associated QT prolongation was amplified in COVID patients compared to uninfected patients, with 10—20% of COVID patients having QT values greater than 500 ms [18].

There are several possible reasons for the increased risk of cardiac toxicity, as suggested by Funck-Brentano et al. [19]. The first could be related to the impact of SARS-CoV2 on the heart. Indeed, coronavirus-infected patients have multiple risk factors for drug-induced rhythm disturbances: frequent hypokalemia and fever, which amplifies drug-induced cardiac channel blockade. In addition, increased IL-6 concentrations observed during infection could be a mechanism of QT prolongation associated with inflammation. According to Guo et al., approximately 30% of inpatients with COVID in a Chinese hospital had myocardial injury associated with cardiac dysfunction and arrhythmias. These myocardial lesions are significantly associated with fatal outcomes [20]. Also, COVID-19 patients were often administered high doses of HCQ in addition to other QT prolongation-inducing drugs (including azithromycin). Indeed, our study highlights several potential 'drug interaction' cases resulting in cardiac adverse effect with HCQ;

80% of the interaction cases involved a combination of HCQ and azithromycin, and all of them resulted in a prolongation of the QT interval. Other drugs such as spiramycin, fluoroquinolones, antivirals, or antidepressants have also caused cardiac damage by interacting with HCQ via a potentiating or additive effect. The seven deaths reported during the COVID period were due to cardiac toxicity (QT prolongation, heart failure, cardiac arrest).

Our study has some limitations and strengths. In the majority of cases, HCQ was associated with other suspected drugs. In addition, not all adverse events are reported to pharmacovigilance centres. In fact, the rate of reporting has been estimated at 90% according to a study by Hazell et al. [21]. There is also a notoriety bias, i.e., once the risk is known and publicized, the rate of reporting of this effect may be increased, which may have happened with HCQ and its cardiac effects during the COVID period. However, during the first weeks of prescription, there were many reports of cardiac toxicity even though it was not an expected effect, which was one of the reasons for the media coverage.

The strength of this study is that it compares data from a single source collected and analysed in the same manner over a 35-year period. Each case is analysed and validated by pharmacovigilance experts before registration.

Conclusion

This study demonstrates that HCQ had a different safety profile in patients treated for COVID-19. Cardiac disorders, for the majority QT prolongation, were the most frequently reported ADRs, which resulted in 40% of cases from an interaction with another drug, especially azithromycin. In the pre-COVID period, the majority of ADRs were cutaneous. The observed difference can be attributed to COVID infection itself, which affects not only the respiratory system but other organs as well, co-medications, and the different profile of the exposed patients.

These data underscore the fact that a drug's safety profile depends on the way it is used. Any drug, even a well-established drug that is believed to be understood, may reveal more frequent and more severe adverse reactions than expected when prescribed outside its MA. Spontaneous reports and pharmacovigilance therefore have a critical role to play in alerting healthcare professionals to potential problems in order to ensure patient safety.

Funding

No funding was received for the preparation of this article.

Data availability statement

Not applicable.

Contributors

All authors contributed to, edited and approved the final version of the manuscript.

Disclosure of interest

The authors declare that they have no competing interest.

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