Hydroxychloroquine safety, comparison between no Covid-19 and Covid-19 patients. Data from the Spanish Pharmacovigilance Database

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Abstract

Aim. To compare the cases reported to the Spanish Pharmacovigilance System (SEFV-H) with HCQ used in COVID-19 vs. HCQ used in other indications. Methods. All cases of adverse drug reactions (ADR) submitted to the Spanish Pharmacovigilance database (FEDRA) from 1 January 1982 to 19 February 2021 suspected to be induced by HCQ were identified. Cases were classified into two groups: no-Covid patients and Covid patients. Frequencies of ADR were compared. Reporting Odds Ratios (ROR) with its lower limit of the 95% confidence interval (-ROR) and Omega () and its lower limit of the 95% credibility interval (-025) were obtained to estimate disproportionalities. Results. More severe cases were reported with the use of HCQ in Covid. Main differences in frequency were observed in hepatobiliary, skin, gastrointestinal, eye, nervous system and heart ADRs. During the Covid-19 pandemic, disproportionality was found for Torsade de Pointes/QT prolongation with a ROR (-ROR) of 132.8 (76.7); severe hepatotoxicity, 18.7 (14.7); dyslipidaemias, 12.1 (6.1); shock, 9.5 (6.9) and ischaemic colitis, 8.9 (2.6). Myopathies, haemolytic disorders and suicidal behaviour increased their disproportionality during the pandemic. Disproportionality was observed for neoplasms, haematopoietic cytopaenias and interstitial lung disease in the pre-Covid period. showed potential interactions between HCQ and azithromycin, ceftriaxone, lopinavir and tocilizumab . Conclusions. The use of HCQ in Covid-19 changed its safety profile. Of particular concern during the pandemic were arrhythmias, hepatotoxicity, severe skin reactions and suicide risk, but not ocular disorders. Some ADRs identified as signals would require more detailed analyses.

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Running head: HYDROXYCHLOROQUINE SAFETY PROFILE

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Authorship statementMS conceptualized, design, acquired data for this study and write the paper. NMK, VV, ZVR, AMF, RSF y LHMA conceptualized the study, reviewed and approved the manuscript.

Data availability statement

The data that support the findings of this study are available from the Spanish Pharmacovigilance System (SEFV-H). Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of SEFV-H.

What is already known about this subject:

HCQ has been used in COVID-19 in a different manner compared with its conventional use.

This is the first study that compare the safety profiles of HCQ according to its pattern of use, in a pharmacovigilance database.

What this study adds:

- The safety profile of HCQ changed when used in Covid-19 patients.
- Hepatic, cardiovascular, and gastrointestinal ADR were more frequents in Covid-19 patients while skin, eye and nervous system disorders were more frequents in noCovid-19 patients.
- Some signals identified need to be confirmed.

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Abstract

Aim. To compare the cases reported to the Spanish Pharmacovigilance System (SEFV-H) with HCQ used in COVID-19 vs. HCQ used in other indications.

Methods. All cases of adverse drug reactions (ADR) submitted to the Spanish Pharmacovigilance database (FEDRA) from 1 January 1982 to 19 February 2021 suspected to be induced by HCQ were identified. Cases were classified into two groups: no-Covid patients and Covid patients. Frequencies of ADR were compared. Reporting Odds Ratios (ROR) with its lower limit of the 95% confidence interval (-ROR) and Omega () and its lower limit of the 95% credibility interval ($_{-025}$) were obtained to estimate disproportionalities.

Results. More severe cases were reported with the use of HCQ in Covid. Main differences in frequency were observed in hepatobiliary, skin, gastrointestinal, eye, nervous system and heart ADRs. During the Covid-19 pandemic, disproportionality was found for Torsade de Pointes/QT prolongation with a ROR (-ROR) of 132.8 (76.7); severe hepatotoxicity, 18.7 (14.7); dyslipidaemias, 12.1 (6.1); shock, 9.5 (6.9) and ischaemic colitis, 8.9 (2.6). Myopathies, haemolytic disorders and suicidal behaviour increased their disproportionality during the pandemic. Disproportionality was observed for neoplasms, haematopoietic cytopaenias and interstitial lung disease in the pre-Covid period. showed potential interactions between HCQ and azithromycin, ceftriaxone, lopinavir and tocilizumab.

Conclusions. The use of HCQ in Covid-19 changed its safety profile. Of particular concern during the pandemic were arrhythmias, hepatotoxicity, severe skin reactions and suicide risk, but not ocular disorders. Some ADRs identified as signals would require more detailed analyses.

Introduction

Hydroxychloroquine (HCQ) was one of the first treatments used for Covid-19 since studies showed promising results [1]–[3]. Nevertheless, later studies did not demonstrate any benefits with HCQ in Covid-19 treatment, and, finally, its use declined all over the world [4],[5].

HCQ is an antimalarial drug derived from quinolone that is safer than chloroquine [6]. With a complex mechanism of action, it has also immunosuppressive effects and is used for arthritis rheumatoid and lupus erythematosus treatment [7]. The most frequent drug adverse effects (ADR) of HCQ include headache, appetite disorders, ocular disturbances – with retinopathies and ophthalmoplegia being the most serious ones -; and gastrointestinal disorders. Serious known ADRs include agranulocytosis, convulsions, deafness, cardiomyopathy, serious skin reactions (i.e. Stevens-Johnson syndrome), myopathy, and suicidal ideation, with the latter being identified during the Covid-19 pandemic. Many of these ADRs are dose dependent and, because HCQ has a narrow therapeutic window, caution is required. Moreover, HCQ can interact with several other drugs. These interactions may be pharmacokinetic or pharmacodynamic in nature. Because polypharmacy is common in elderly patients and HCQ is usually administered more frequently in this population, it is likely that drug-drug interactions contribute to the ADR risk increment [8]. Altogether, these factors may have changed HCQ safety profile as known before the Covid-19 pandemic outburst.

The aim of this study was to compare ADR cases related to HCQ when used for Covid-19 treatment with cases in other indications as reported to the Spanish Pharmacovigilance System (SEFV-H).

Methods

Descriptive analytic study in a nationwide pharmacovigilance database.

Data source and study period

We used FEDRA, the Spanish Pharmacovigilance database, to identify all the ADR cases related to HCQ. This database includes all ADRs reported to the Spanish Pharmacovigilance System (SEFV-H). Health professionals, pharmaceutical industry and the public submit spontaneous reports of suspected ADRs. Then, ad hoc committees evaluate reports using an algorithm [9] to determine whether a causal relationship exists. Nevertheless, information coming from the reports is included in the database regardless of causality and severity. ADRs are coded according to the Medical Dictionary for Regulatory Activities dictionary (MedDRA) [10].

The study period was defined from 1 January 1982 to 19 February 2021. Likewise, we considered a pre-pandemic period the period before 1 March 2020 and a pandemic period from 1 March 2020 on.

Cases identification

We identified all reports including HCQ as a suspected drug. There were no restrictions by age or gender. Indications for HCQ were screened manually to define two categories as follows: no-Covid treatment and Covid treatment. Cases within the pre-pandemic period were all considered no-Covid treatment, whilst cases during the pandemic without indication were deemed unknown, and, therefore, they were discarded for the analysis.

Statistical analysis

Reporting frequencies were estimated for the following variables: gender, age group, seriousness, mortality, HCQ dose, HCQ treatment length, HCQ indication, concomitantly used medications, as well as type of ADR grouped by MedDRA system and organ classification (SOC). SPSS v24 and Excel programme were used for this purpose.

When possible, daily doses of HCQ were estimated based on posology. Incomplete posologies that did not allow daily dose to be estimated were considered unknown. Daily doses were categorised into three levels: low (400 mg /day), medium (400-600 mg/day), and high (800 mg/day). Also, total administered dose was estimated and categorised as follows: low ([?] 50.000 mg), medium (51,000-200,000 mg), and high ($>$ 200,000 mg)

For each period, the disproportionality analysis was carried out based on the FEDRA database "Signal generation module". The Reporting Odds Ratio (ROR) was obtained to estimate disproportionality of the different ADRs reported with HCQ [11]. We used a case/non case approach to determine the strength of the association between HCQ and whichever ADR. The lower limit of the 95% confidence interval was -ROR. We considered a potential HCQ-ADR association when - ROR was higher than 1 and there were at least 3 cases reported. Standardised MedDRA Queries (SMQ) from MedDRA were used to identify ADRs. SMQs are validated pre-determined sets of MedDRA terms grouped together that are associated with a specific medical condition [12] . We identified the HCQ-ADR associations with at least 3 reported cases and with the lower confidence interval (IC 95%) larger than 1 in at least one of the periods of interest.

To explore potential interactions, Omega () statistic was obtained. This analysis compares the observed relative reporting rate of a given ADR, granted that the reports include the co-existence of two drugs, with its expected value estimated based on the relative reporting rates of the ADR for each drug separately. The observed number of cases is the number of reports in FEDRA for the two drugs together that include the ADR of interest. When is positive, then the drug-drug-ADR association is reported more often than expected [13]. The lower limit of the 95% credibility interval is referred to as $_{-025}$. We considered a potential drug-drug interaction to exist when $_{-025}>0$.

For the disproportionality analysis, exposure to a given drug was defined as the recording of the drug in a report, whether or not it was suspected of causing the reaction.

Results

During the periods under investigation, the SEFV-H received 417,484 cases of suspected ADRs, of which, 382,201 cases were notified during the pre-pandemic and 35,283 during the pandemic period (01/03/2020 to

19/02/2021). Of these 417,484 cases of suspected ADRs, in 635 (0.15%) HCQ was reported as the suspected medication. HCQ was first reported to SEFVH in 1991. During the pandemic period, there was an 18.3-fold increase in notifications including HCQ as the suspected drug.

In 366 cases, HCQ was used to treat Covid-19 (58% of all cases with HCQ), whereas in 265 cases HCQ was administered for the treatment of diseases other than Covid-19. In 4 cases, all of them within the pre-pandemic period, HCQ indications were unknown. Consequently, these 4 cases were discarded for analyses. Therefore, our sample was composed of 631 cases in which HCQ was the suspected medication.

Features of notified cases

Table 1 displays the general features of cases. Of 635 cases of interest, 87% relied on spontaneous reporting. Seventy-two per cent (72%) of cases were directly submitted to SEFV-H by healthcare professionals, while 2% were reported by the public, 38% by the pharmaceutical industry, and 4% came from medical literature reviews. It is of note that a single case could have different origins. Most of cases (76%) directly submitted to SEFV-H by healthcare professionals were reported from a hospital.

Seventy-two per cent (72%) of cases were serious, and the clinical outcome was fatal in 5% of cases. Fifty-six per cent (56%) of patients were females. Patients' age range and median age were 0,25 – 96 and 59 years, respectively. Sixty-three per cent (63%) of patients were adults, and 31% were $>$ 65 years. In the no-Covid cases, the conditions for which HCQ was most frequently used were arthropathies (34%) and lupus erythematosus (32%). In none of the notified cases, neither prophylaxis nor treatment for malaria was the HCQ indication. In 41% of cases, the daily administered HCQ dose was lacking. Of the remaining cases, in 33% medium daily doses (i. e. 400-600 mg/day) were given, low doses in 20 %, and high doses in 6%. Of high daily doses, 100% were administered to Covid patients. The median total accumulated dose was 2,800 mg, though there were significant differences between the two groups. Most of patients (43%) received a low total HCQ dose. With respect to total cumulative dosis, all the medium / high total HCQ doses were given to no-Covid patients, since these patients were treated with HCQ for longer.

Other medications included in the reports

The reported cases included a total of 2,263 drugs, including HCQ. Accordingly, on average, each patient was administered 3.6 medications, and the number of drugs given to Covid patients was larger than that given to their no-Covid counterparts. More than 90% of Covid patients took more than one medication relative to the group of no-Covid patients, in which this percentage was less than 50%. Table 1 displays the groups of drugs that were most frequently notified together with HCQ. Figure 2 shows, according to their active ingredient, the drugs notified along with HCQ that were deemed to be suspected either by themselves or due to their potential interactions.

Reported adverse drug reactions

Organs and systems most frequently affected in reported cases were as follows: hepatobiliary disorders (133 cases, 21%), gastrointestinal disorders (124 cases, 20%), skin and subcutaneous tissue disorders (123 cases, 19%), and cardiac derangements (80 cases, 13%). Figure 3 shows the distribution of the involved organs / systems according to the corresponding percentages of notified cases separately for Covid and no-Covid patients.

Disproportionality analysis

Table 2 shows the disproportionality analysis results for the ADRs for which a statistically significant association was found in one of the two periods. As shown, for certain ADRs there were differences between these two periods. There were some statistically significant associations with several ADRs in the pandemic period, but not in the previous period. Such was the case of cardiac arrhythmias, to be more specific, the *Torsade de Pointes* /QT prolongation (TdP/QTp) with a ROR (-ROR) equal to 132.8 (76.7) and 39 cases reported during this period; severe hepatic disorders, 18.7 (14.7); dyslipidaemias, 12.1 (6.1); shock, 9.5 (6.9); and ischaemic colitis, 8.9 (2.6). In the pre-pandemic period, there was a statistically significant association with

a number of malignancies, haematopoietic cytopaenias, agranulocytosis, and interstitial pulmonary disease, with the following ROR (-ROR) values: 2.3 (1.3), 2.5 (1.7), 3.2 (1.9), 5.0 (2.6), respectively. Some ADRs presented statistically significant disproportion in both periods, though their incidence was higher during the pandemic period. Some example of this are rhabdomyolysis/myopathy, which ROR increased from 5.2 to 8.0; haemolytic disorders (from 3.6 to 6.6), and suicidal/self-injury behaviour (from 3.1 to 5.9). On the contrary, in the case of retinal disturbances, statistical disproportion dropped from 15.4 in the pre-pandemic period to 5.1 in the pandemic period.

Concerning the analysis on the potential interactions (see Table 3), the statistic, as estimated for the most frequently reported active ingredients and the most relevant ADRs, indicated that some ADRs could be increasing with the use of HCQ concomitantly with other drugs as follow: azithromycin, ceftriaxone or lopinavir for TdP/QTp; azithromycin, ceftriaxone and tocilizumab for hepatic disorders, and azithromycin and ceftriaxone for dyslipidaemias. These interactions were not found in the period before the Covid-19 pandemic outburst.

Discussion

The use of HCQ early in the Covid-19 pandemic resulted in a substantial increase in suspected ADR reporting associated with this medication. The rise in HCQ use [14][15]–[17], along with the concerns about its administration to Covid patients in spite of the lack of sufficient scientific evidence, and the fact that everybody's eyes were focused on any aspects related to the pandemic because of the worldwide mass media coverage may have played a part in this increment in suspected ADR reporting. The subsequent decline in reporting is likely to be related to calls to caution [7] as well as to the publication of findings against HCQ [4],[5].

Both the patient profile and HCQ use pattern proved different in our two groups (i. e, Covid and no-Covid patients). In the case of no-Covid patients, the cases most often corresponded to middle-aged women treated with low daily HCQ doses in a majority of cases. These patients did not receive high daily doses ([?] 800 mg/day), even though the total administered dose was considerably higher (median: 21,600), which is consistent with the fact that the treatment length was substantially longer. It should be underscored that, in both groups, a high percentage of case notifications did not include any data on the administered doses. Though important, the completion of the box 'Administered doses' in the report form is not obligatory to validate the notifications submitted to SEFV-H. As expected, the main indications were rheumatic conditions, arthropathies, and lupus erythematosus; however, we also found off-label HCQ indications. Nearly half of patients took only HCQ, and reported co-medications were principally corticoids, other immunosuppressants, and painkillers. By active ingredient, methotrexate, prednisone, enoxaparin, and mycophenolate were the most frequently administered to these patients. Most of cases of Covid patients were males, aged approximately a decade over their no-Covid counterparts, who, in a majority of cases, were given medium daily HCQ doses, and a low total dose in 100% of cases, a finding that is consistent with the fact that the length of their treatment was considerably shorter. Virtually all patients were treated with medications other than HCQ, notably antimicrobials, corticoids, and immunosuppressants. By active ingredient, azithromycin and the lopinavir+ritonavir combination were the most frequently combined with HCQ in a high percentage of Covid patients. This finding mirrors the kind of patients who were treated with HCQ as well as the usual HCQ administration guidelines [7],[18],[19]. These differences in patient features, indications, HCQ doses and treatment length and use of medications other than HCQ have by themselves the potential to change the safety profile of the drug, as was the case of the modifications of ADR profile we found in our study.

Firstly, there was a 24% excess of serious cases among Covid patients. Covid patients on HCQ were, by definition, persons who have been admitted to a hospital, and, therefore, it is assumed that they suffer from a more serious disease, which may contribute to explain why Covid patients in our study were in worse health condition. On the other hand, because of the work overload of hospital healthcare professionals in Spain in that time, it is reasonable to assume that only the most severe ADRs were reported to the pharmacovigilance system. The overall profile of ADRs potentially associated with HCQ we found in no-Covid patients approximated to that in earlier studies [7],[20]. In no-Covid patients on HCQ, the prevailing ADRs

are cutaneous in nature, followed by eye disorders, general health problems, nervous system disturbances, and gastrointestinal disorders; while in Covid patients the most frequent ADRs are hepatobiliary disorders, followed by gastrointestinal, cardiac, general disorders and intoxications, and skin disorders. Importantly, in the present study, the main differences between the two groups corresponded to hepatobiliary, gastrointestinal, ocular and cardiac disorders, which are usually reported more frequently in Covid cases, on the one hand, and skin and nervous system disorders, the reporting frequency of which was higher in no-Covid cases, on the other (Figure 3).

The percentage of hepatobiliary disorders reported among the Covid cases is a striking finding in our study. According to the reports released by SEFV-H during the Covid-19 pandemic, most of hepatobiliary disorder notifications came from only a single hospital, in which active pharmacovigilance surveillance specifically for hepatotoxicity was conducted [21], therefore hepatobiliary ADRs might be overrepresented. Furthermore, it should be borne in mind that SARS-Cov-2 infection itself is associated with liver damage [22], which suggests that, in our study, this finding may be flawed by an indication bias. Nevertheless, earlier studies have also reported hepatobiliary disorders to rank either first or second in frequency among Covid patients on HCQ, particularly when this drug is combined with other medications [23]–[25]. The disproportionality analysis we conducted showed that there was an association between HCQ treatment and both overall liver and severe liver disturbances only during the pandemic period (Table 2).

Additionally, gastrointestinal disorders are reportedly the most frequent ones upon HCQ treatment initiation. This holds true for both Covid and no-Covid patients [26]. In our study, the gastrointestinal tract is the second most frequently involved system in Covid patients on HCQ, which is in line with the results from a Portuguese prospective study [23]. Indeed, in our study, HCQ treatment in Covid patients is associated with "non-infectious diarrhoea", "ischaemic colitis" and "gastrointestinal perforation, ulceration, haemorrhage or obstruction" (see Table 2). Of note, the latter HCQ gastrointestinal disturbance had not been reported anywhere before Covid-19 pandemic [7].

Cardiac involvement represented one of the major safety concerns when HCQ was used for Covid treatment, especially given its use in combination with azithromycin.. [27]. In the present study, cardiac derangements have been reported to occur twice more frequently in Covid patients as compared with their no-Covid counterparts. In fact, according to disproportionality analysis results, three cardiac disturbances ranked first, second and third, with cardiac arrhythmias, specifically TdP/QTp, ranking first; and this was the heart problem for which we found the largest number of differences in relation to disproportion between the two patient groups (Table 2). This striking increase in TdP/QTp in these patients may result from the use of higher HCQ doses [26] or, alternatively, may be due to the use of concomitant medications such as azithromycin [27], as shown by the Ω statistic estimation (Table 3). Likewise, it is an outstanding finding that the summaries of product characteristics of some of the drugs currently commercialised in Spain that contain HCQ do not include this risk in spite of mass media information impact and safety statements released by both regulatory authorities and scientific societies [7],[28]. Concerning cardiomyopathy, which was a cardiac ADR reported in our study, we did not find any important differences in ROR for the two groups of patients, despite cardiomyopathy was associated with lengthy treatment with HCQ [26].

When HCQ was first used as a therapy for COVID-19, another cause of concern was the attendant risk of retinopathy. Although this is an infrequent complication, eventually it can cause irreversible blindness. According to current evidence, retinopathy is related to HCQ dose and treatment length. So, the most recent clinical guidelines recommend not to exceed 5mg/kg body weight/day in order to prevent this HCQ therapy complication [19]. In Spain, with a patient mean weight of 70 kg, this recommendation would correspond to a dose of 350 mg/day. In our study, most of doses given to Covid patients exceeded this figure. Nonetheless, we found that retinopathy was more prevalent in no-Covid patients in both frequency and disproportionality. Therefore, it could be assumed that the risk of eye disturbances is more strongly associated with HCQ treatment length than is with the dose, which would be in keeping with results from earlier studies [26].

Skin reactions have been reported most frequently in HCQ treatment for no-Covid patients. They are well

established reactions in patients on HCQ, and may become apparent in the form of rashes, itching and/or hyperpigmentation. However, some of these skin adverse reactions may be more worrying, as is the case of Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP). In some cases, they manifest themselves with psoriatic lesions and hair loss or discoloration [7],[29]. Such HCQ-related skin reactions can be classified according to the accumulated dose, the most common being reactions that become apparent following the administration of high accumulated doses [29], which is in keeping with our finding that skin adverse reactions were most often reported in patients undergoing prolonged HCQ therapy, that is, in no-Covid patients. However, when looking at severe skin reactions, including blistering and exfoliative conditions, we noted that these reactions were notified relatively more frequently in Covid patients, and furthermore ROR was higher in the pandemic period (Table 2). HCQ accumulated dose range in which skin reactions appear is very broad. In fact, such reactions may become evident with accumulated doses as low as 3,000 or 4,000 mg, as is the case of some severe skin complications such as AGEP or Drug reaction with eosinophilia and systemic symptoms (DRESS) [29]. Thus, it can be speculated that HCQ-related skin reactions in the setting of COVID-19 therapy either were less frequent but more severe or, alternatively, only the most severe reactions were notified.

The evidence on the risk of suicidal/self-injury behaviour has been conflicting, and, up to date, there has been insufficient evidence concerning the relationship of these psychiatric conditions to HCQ use [30]. However, during the Covid-19 pandemic, it was one of the causes of concern that led to change the summary of product characteristics of HCQ. [31],[32]. While few cases had been reported during the pre-pandemic period, this signal could have been detected at that time. (Table 2).

Aside from the aforementioned psychiatric, hepatic and gastrointestinal disorders and cardiac arrhythmias, we found further ADRs associated with the use of HCQ in Covid patients that are usually overlooked or not are observed so distinctly when HCQ is used for other indications, such as dyslipidaemias, shock, ischaemic colitis, kidney disturbances, noninfectious encephalopathy, and acute renal failure (Table 2). During the pre-pandemic period, it had been reported malignant adverse reactions, which may be explained by HCQ immunomodulatory effects. However, these malignant ADRs should be interpreted cautiously. Likewise, cytopaenias, including agranulocytosis, are well known HCQ adverse reactions. Their disproportionality is lower in Covid patients, which may be due to a shorter exposure time to the drug in these patients. Concerning dyslipidaemias, it is remarkable that, in our study, in all cases HCQ was given concomitantly with lopinavir + ritonavir, medications for which dyslipidaemias are well established ADRs. Therefore, it is reasonable to assume that, in the present study, the use of lopinavir + ritonavir was a confounding factor. Alternatively, these ADRs might be due to a true interaction, a possibility suggested by the results we found with the statistic.

We obtained significant estimators for interactions that, curiously enough, only were found when HCQ was used to treat Covid patients. Some of these interactions are known, such as the risk of TdP/QTp with the concomitant use of azithromycin and, to a lesser extent, lopinavir and ceftriaxone. On the contrary, other interactions are less known or even unknown, like severe hepatic derangements and dyslipidaemias.

Pharmacovigilance database-based studies are flawed with obvious limitations. The major drawback is probably under-reporting, which, tough difficult to accurately estimate, has been reported to be as high as 90% [33]. This, along with the lack of data on the comsuption of the drug in question, prevent from accurately estimating the actual incidence of the reported ADRs. Furthermore, the number of cases notified to the database largely relies on a series of factors, such as the involved medication (commercialisation time, use in the clinical setting, current knowledge on the drug and so forth), and the reporting person's profile (available time, knowledge, expertise, and degree of commitment with routine pharmacovigilance activities, etc.). Additionally, the relevance and impact of all these limiting factors may vary with time or other circumstances, as it was the case with Covid-19 pandemic. No doubt, public's interest and concern, along with the mass media focus, have markedly influence on ADR reporting during the pandemic. On the other hand, it should be kept in mind that the Covid-19 pandemic had a major impact on the Spanish healthcare system running. However, it is not possible to precisely understand the impact this factor had on the ADR

spontaneous reporting system and the pharmacovigilance databases. Finally, the lacking clinical data in notification forms is another constraint to be considered.

Still, spontaneous reporting systems presents several advantages: they cover all types of authorised drugs; it is a simple, quick and economical method enabling to generate hypotheses and identify new potential safety concerns involving drugs, notably rare, infrequent or unexpected events. Several studies showed that, despite their shortcomings, spontaneous reporting systems have the potential to identify early and efficiently emergent risks associated with the use of medications [34]–[37].

Conclusions

The way in which HCQ has been used during the Covid-19 pandemic has resulted in a change in its safety profile. This change has reflected in the SEFV-H database. Of particular concern, there has been an increase in reporting disproportionality for cardiac arrhythmias, severe hepatotoxicity, severe skin reactions, and suicidal risk. HCQ-related eye disturbances seem to be mostly related to the prolonged use of the drug. In the setting of the clinical HCQ use in Covid patients, we identified the following signals: dyslipidaemias and some severe gastrointestinal conditions, such as ischaemic colitis. On the contrary, the signals identified for HCQ use in no-Covid patients were malignancies and pulmonary interstitial disease. However, these findings should be interpreted with caution, since they would need to be subjected to a detailed analysis of the aggregate cases enabling to formulate firmly based hypotheses. Furthermore, our findings need to be replicated with appropriate observational studies allowing confirming the hypotheses that eventually can be derived from the present study.

Statement

FEDRA is the Spanish Pharmacovigilance System of Human Medicines (SEFV-H) database and is managed by the Spanish Medicines and Health Products Agency (AEMPS). The information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases. The discussion and conclusions of this study are the authors' responsibility and do not represent the opinion of the SEFV-H or the AEMPS.

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Table 1. Characteristics of the reported cases

		All cases (N=631)	**No-Covid patients (N=265)**	**Covid patients (N=366)**	**P**
Seriousness – no. (%)	Seriousness – no. (%)				
	Serious cases	454 (72)	153 (58)	301 (82)	<0.001
	Deaths	30 (5)	8 (3)	22 (6)	.058

		All cases (N=631)	**No-Covid patients (N=265)**	**Covid patients (N=366)**	**P**
Gender – no. (%)	Gender – no. (%)				
	Females Males Unknown	355 (56) 267 (42) 9 (1)	219 (83) 39 (15) 7 (3)	136 (37) 228 (62) 2 (1)	<0.001
Age – yr.	Age – yr.				
	Median (IQR[a])	59 (45 – 70)	50.0 (36.8 – 65.0)	61.0 (51.0 – 72.0)	<0.001
Age group – no. (%)	Age group – no. (%)				
	Newborn Breastfed Child Adolescent Adult > 65 years Unknown	4 (1) 2 (0) 8 (1) 3 (1) 395 (63) 198 (31) 21 (3)	4 (2) 1 (0) 5 (2) 2 (1) 180 (68) 55 (21) 18 (7)	0 (0) 1 (0) 3 (1) 1 (0) 215 (59) 143 (39) 3 (1)	
Daily HCQ dose – no. (%)	Daily HCQ dose – no. (%)				
	Low, < 400 mg /d Medium, 400-600 mg/d High, 800 mg/d Unknown	126 (20) 209 (33) 37 (6) 259 (41)	111 (42) 47 (18) 0 (0) 107 (40)	15 (4) 162 (44) 37 (10) 152 (41)	<0.001
Total HCQ dose – mg	Total HCQ dose – mg				
	Median (IQR)	2,800 (1,600 - 5,900)	21,600 (5,400 – 87,800)	2,400 (1,600 – 3,100)	<0.001
Total HCQ dose – no. (%)	Total HCQ dose – no. (%)				
	Low ([?] 50.000 mg) Medium (51.000-200.000 mg) High (> 200.000 mg) Unknown	271 (42.9) 14 (2.2) 16 (2.5) 330 (52.3)	63 (23.8) 14 (5.3) 16 (6.0) 172 (64.9)	208 (56.8) 0 (0) 0 (0) 158 (43.2)	<0.001
Length of treatment with HCQ – days, no. (%)	Length of treatment with HCQ – days, no. (%)				
	Median (IQR)	7 (5 - 17)	65 (18 - 365)	6 (4 - 7)	<0.001
	Short ([?] 10 days) Medium (11-90 days) Long (> 90 days) Unknown	283 (44.8) 73 (11.6) 61 (9.7) 214 (33.9)	20 (7.5) 51 (19.2) 59 (22.3) 135 (50.9)	263 (71.9) 22 (6.0) 2 (0.5) 79 (21.6)	<0.001
Indications – no. (%)	Indications – no. (%)				

		All cases (N=631)	**No-Covid patients (N=265)**	**Covid patients (N=366)**	**P**
	Covid19 Arthropathy Lupus erythematosus Sjögren's syndrome Dermatomyositis Connective tissue disorder Lichen Alopecia Antiphospholipid syndrome Collagen disorder Polymyositis Cutaneous sarcoidosis Others[b] Unknown	366 (58) 90 (14) 84 (13) 9 (1) 6 (1) 5 (1) 5 (1) 5 (1) 3 (1) 2 (0) 2 (0) 2 (0) 10 (2) 42 (7)	0 (0) 90 (34) 84 (32) 9 (3) 6 (2) 5 (2) 5 (2) 5 (2) 3 (1) 2 (1) 2 (1) 10 (3) 42 (16)	366 (100) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0) 0 (0)	
Total drugs - no. (%)	Total drugs - no. (%)				
	Median (IQR) 1 drug (only HCQ) 2-10 drugs > 10 drugs	3.0 (2 - 4) 157 (24.9) 456 (72.3) 18 (2.9)	1.0 (1 - 4) 136 (51.3) 125 (47.2) 4 (1.5)	4.0 (3 - 5) 21 (5.7) 331 (90.4) 14 (3.8)	<0.001
More frequent pharmacologic groups – no. (%)	More frequent pharmacologic groups – no. (%)	More frequent pharmacologic groups – no. (%)			
	antibacterials antivirals corticosteroids immunosuppressants (IL inhib.) immunosuppressants antithrombotics analgesics drugs for peptic ulcer	79 (44) 204 (32) 119 (19) 85 (13) 76 (12) 62 (10) 60 (10) 44 (7)	10 (4) 0 (0) 63 (24) 5 (2) 57 (22) 18 (7) 23 (9) 18 (7)	269 (73) 204 (32) 119 (19) 85 (13) 76 (12) 62 (10) 60 (10) 44 (7)	

[a] IQR: Interquartile Range; [b]Others (1 case each): Hyperparathyroidism, Autoimmune disorder, Sjögren-Larsson Syndrome, Sprain, Psoriasis, Rheumatic disorder, Photosensitivity disease and photodermatosis, Whipple's Disease, Schnitzler's Syndrome, Polyserositis; * $p < 0.05$

Table 2. Disproportionality observed for some ADRs, (- ROR> 1, n[?] 3 in at least one of the periods considered –)

	Pre-pandemic (01-01-82 a 29-02-20)	**Pre-pandemic (01-01-82 a 29-02-20)**	**Pandemic (01-03-20 a 19-02-21)**	**Pandemic (01-03-20 a 19-02-21)**
Adverse Reaction (SMQ narrow, MedDRA 24.0)	**No cases**	**ROR (-ROR)[a]**	**No cases**	**ROR (-ROR)**
Torsade de Pointes / QT prolongation	2	3.5 (0.9)	39	132.8 (76.7)
Cardiomyopathy	9	25.5 (13.1)	5	26.0 (9.1)
Cardiac arrhythmias	7	1.9 (0.9)	51	20.3 (14.6)
Drug related hepatic disorders - severe events only	8	0.8 (0.4)	103	18.7 (14.7)
Hepatic disorders	16	1.0 (0.6)	135	17.1 (13.8)
Dyslipidaemia	0	NA	10	12.1 (6.1)
Shock	8	1.1 (0.5)	47	9.5 (6.9)
Ischaemic colitis	0	NA	3	8.9 (2.6)
Severe cutaneous adverse reactions	15	3.2 (1.9)	23	8.8 (5.6)
Rhabdomyolysis/myopathy	8	5.2 (2.6)	5	8.0 (3.1)
Haemolytic disorders	3	3.6 (1.1)	3	6.6 (2.0)
Suicide/self-injury	4	3.1 (1.2)	6	5.9 (2.6)
Cardiac failure	3	1.6 (0.5)	7	5.5 (2.5)
Toxic-septic shock conditions	2	2.8 (0.7)	4	5.3 (1.9)
Retinal disorders	15	15.4 (9.2)	7	5.1 (2.3)
Chronic kidney disease	2	1.6 (0.4)	6	4.6 (2.0)
Noninfectious encephalopathy/delirium	1	0.6 (0.1)	5	4.3 (1.7)
Noninfectious meningitis	3	4.5 (1.4)	2	3.8 (0.9)
Pulmonary hypertension	3	13.0 (4.1)	1	3.6 (0.5)
Respiratory failure	3	1.0 (0.3)	7	3.4 (1.6)
Acute renal failure	4	0.7 (0.3)	14	3.3 (1.9)
Hearing impairment	8	4.7 (2.3)	5	3.2 (1.3)

	Pre-pandemic (01-01-82 a 29-02-20)	**Pre-pandemic (01-01-82 a 29-02-20)**	**Pandemic (01-03-20 a 19-02-21)**	**Pandemic (01-03-20 a 19-02-21)**
Gastrointestinal perforation, ulceration, haemorrhage or obstruction	6	0.6 (0.3)	14	2.7 (1.6)
Sepsis	4	3.3 (1.2)	4	2.7 (1.0)
Infective pneumonia	7	3.1 (1.5)	6	2.2 (1.0)
Noninfectious diarrhoea	12	0.6 (0.3)	37	2.1 (1.5)
Malignant lymphomas	4	7.2 (2.7)	1	1.7 (0.2)
Haematopoietic cytopenias	30	2.5 (1.7)	14	1.2 (0.7)
Ocular motility disorders	3	4.4 (1.4)	1	1.2 (0.2)
Pregnancy and neonatal topics	18	5.2 (3.2)	5	1.2 (0.5)
Agranulocytosis	14	3.2 (1.9)	4	1.1 (0.4)
Opportunistic infections	8	3.6 (1.8)	3	1.0 (0.3)
Malignancies	11	2.3 (1.3)	1	0.2 (0.0)
Interstitial lung disease	9	5.0 (2.6)	0	NA

[a] SMQ: Standardized ROR: Reporting Odds Ratio; -ROR: lower limit of the 95% confidence interval for the ROR

Table 3. Disproportionality for HCQ-drug interactions and the most relevant ADRs (Omega statistic, Ω)

ADR (SMQ)	Interacting drug	Ω ($\Omega_{0.025}$)[a]	Ω ($\Omega_{0.025}$)[a]	Ω ($\Omega_{0.025}$)[a]
		Total	**Pre-Covid**	**Post-Covid**
TdP/QTp[b]	azithromycin	3.00 (2.41)	-0.04 (-10.37)	1.67 (1.08)
	ceftriaxone	1.10 (0.20)	-0.11 (-10.43)	0.07 (-0.84)
	lopinavir+ritonavir	2.48 (1.85)	0.00 (-10.32)	0.72 (0.09)
	tocilizumab	0.72 (-0.49)	-0.12 (-10.44)	-0.12 (-1.33)
Cardiomyopathy	azithromycin	-0.78 (-3.37)	-0.12 (-10.45)	-0.35 (-2.94)
	ceftriaxone	-2.67 (-12.99)	-0.19 (-10.51)	-2.44 (-12.76)
	lopinavir+ritonavir	-1.55 (-5.33)	0.00 (-10.32)	-1.36 (-5.14)
	tocilizumab	-2.20 (-12.53)	-0.42 (-10.75)	-1.84 (-12.16)
Drug related hepatic disorders - severe events only	azithromycin	2.08 (1.68)	-0.21 (-10.54)	0.91 (0.52)
	ceftriaxone	0.66 (0.14)	-0.77 (-11.09)	-0.17 (-0.70)
	lopinavir+ritonavir	-1.33 (-2.20)	0.00 (-10.32)	-2.42 (-3.29)
	tocilizumab	1.89 (1.36)	-0.41 (-10.73)	0.80 (0.26)
Dyslipidaemia	azithromycin	1.88 (0.47)	-0.01 (-10.34)	0.67 (-0.74)
	ceftriaxone	2.38 (0.96)	-0.02 (-10.34)	0.93 (-0.48)
	lopinavir+ ritonavir	1.02 (-0.12)	0.00 (-10.32)	2.83 (1.69)

ADR (SMQ)	Interacting drug	Ω ($\Omega_{0.025}$)[a]	Ω ($\Omega_{0.025}$)[a]	Ω ($\Omega_{0.025}$)[a]
	tocilizumab	-0.82 (-4.61)	-0.24 (-10.56)	-1.26 (-5.05)

[a] estimated from the drug commercialisation date (azithromycin: 01/12/1992; ceftriaxone: 01/05/1999; lopinavir: 13/06/2001; tocilizumab: 27/01/2009; [b]TdP/QTp: Torsade de Pointes/QT prolongation (SMQ)

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